**Synthesis of Sultams and Related Sulfur Heterocycles Using the**

**Ring-Closing Metathesis Reaction**

María del Sol Jiménez

B. S., University of Puerto Rico, 2001

Submitted to the Department of Chemistry and the Faculty of the Graduate School of the University of Kansas in partial fulfillment of the requirements for the degree of Doctor of Philosophy

_____
Paul R. Hanson, *chairperson*

_____
Helena C. Malinakova

_____
Jon Tunge

_____
Robert G. Carlson

_____
Lester A. Mitscher

Date Defended:_____

The Dissertation Committee for María del Sol Jiménez
certifies that this is the approved version of the following dissertation:

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_____
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_____
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Date Approved: _____

**Abstract**

*María del Sol Jiménez, Ph. D.*

Department of Chemistry

University of Kansas

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The use of ring-closing metathesis (RCM) for the construction of small, medium and large rings has become a powerful tool in organic chemistry. The application of this reaction for the construction of sulfur heterocycles (*S*-heterocycles) as potential pharmacological targets has become a major focus in our laboratories. The goal of this dissertation is to demonstrate the application of RCM for the construction of a variety of sulfur heterocycles including sultams, cyclic sulfamides, cyclic sulfamoyl carbamates and cyclic sulfamoyl ureas with the ultimate goal of biological screening. The successful synthesis of 6- to 11-membered ring *S*-heterocycles using this method will be discussed.

The first project described in this dissertation involves the use of RCM for the construction of 6-membered ring sultams with multiple handles for further functionalization and library development. The utility of these sultams as versatile scaffolds for a variety of diversification reactions using solution-phase chemistry will be explained. Also, the successful application of ROMP-derived reagents developed in our laboratories as facilitated protocols for diversification strategies and subsequent library development will be discussed.

The second project describes the use of RCM for the facile construction of sulfamide analogs of the HIV protease inhibitor DMP 323. The accomplishment of both symmetric and unsymmetric cyclic sulfamides will be discussed. Also, efforts towards the synthesis of *N*-hydroxy cyclic sulfamides will be presented.

The third project describes the use of RCM for the construction of 9-membered ring sulfamoyl ureas and 9- to 11-membered ring sulfamoyl carbamates.

***To Mom and Dad, for all your support and unconditional love……..***

***……...and to Chad, the best part of my life……***

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Mom, you are an amazing human being. You have been my main support in every decision I have made, even when that meant being away from you. You are the most important person in my life, my best friend. Without your understanding, support unconditional love and everything you have taught me I will never be the person I am today. I thank you for everything you have sacrificed for me and for being so wonderful. Remember that even when I am away, you are always in my heart.

Dad, my wine and coffee partner, thanks for teaching me that hard work will always lead to great rewards even when sometimes we cannot see it right away. Thanks for being patient and supporting me 100% while in grad school. You have taught me that you don't have to be the best, but be the best that you can possibly be. Your words of wisdom have been a valuable gift to me, mostly during my most difficult days. You have so much confidence in me Dad! Thanks for cheering me up when I felt down and for always making my times at home unforgettable.

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To my dear friends Jennifer and Punitha, you have been the best friends anyone could ask for. I wish you the best in each of your careers and always keep in mind that the sky is the limit. I will forever cherish your friendship and hope we will keep in touch.

**Synthesis of Sultams and Related Sulfur Heterocycles Using the Ring-Closing Metathesis Reaction**

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## Abbreviations

| | |
|---|---|
| Å | angstrom |
| Ac | acetyl |
| $Ac_2O$ | acetic anhydride |
| AcOH | acetic acid |
| ADDP | 1,1'-(azodicarbonyl)dipiperidine |
| AgOTf | oxo(trifluoromethylsulfonyl)silver |
| AIBN | 2,2'-azo bisisobutyronitrile |
| $AlCl_3$ | aluminium chloride |
| $Al_2CO_3$ | aluminum carbonate |
| Ar | aryl |
| BHT | 2,6-di-*t*-butyl-*p*-cresol |
| Bn | benzyl |
| Boc | *tert*-butoxycarbonyl |
| Bu | butyl |
| $Bu_4NCl$ | tetrabutylammonium chloride |
| *n*-BuLi | butyllithium |
| $Bu_3SnH$ | tributyltin hydride |
| *t*-Bu | *tert*-butyl |
| Bz | benzoyl |
| CAN | ceric ammonium nitrate |
| cat. | catalyst/catalytic |

| | |
|---|---|
| cm | centimeter |
| $CDCl_3$ | chloroform (deuterated) |
| $CH_2Cl_2$ | methylene chloride |
| $Cl_3CCN$ | trichloroacetonitrile |
| $ClSO_2OH$ | chlorosulfuric acid |
| $CH_3CN$ | acetonitrile |
| CML | chronic myelogenous leukemia |
| $Cs_2CO_3$ | cesium carbonate |
| CSI | chlorosulfonyl isocyanate |
| $SO_2Cl_2$ | sulfuryl chloride |
| d | day(s) |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCC | dicyclohexyl carbodiimide |
| DCE | 1,2-dichloroethane |
| DDQ | 2,3-dichloro-5,6-dicyano-1,4-benzoquinone |
| DEAD | diethyl azodicarboxylate |
| DIAD | diisopropyl azodicarboxylate |
| DIPA | diisopropylamine |
| DMAP | 4-(dimethylamino)pyridine |
| DME | 1,2-dimethoxyethane |
| DMF | *N*,*N*-dimethylformamide |
| DMSO | dimethyl sulfoxide |

| | |
|---|---|
| dr | diastereomeric ratio |
| E | electrophile |
| ee | enantiomeric excess |
| EI | electron impact |
| equiv. | equivalent(s) |
| Et | ethyl |
| EtOH | ethanol |
| $EtAlCl_2$ | ethylaluminum dichloride |
| $Et_3N$ | triethylamine |
| FAB | fast atom bombardment |
| GC | gas chromatography |
| h | hour(s) |
| HCl | hydrochloric acid |
| $H_2O$ | water |
| HIV-1 | human immunodeficiency virus type 1 |
| $HCO_2^-NH_4^+$ | ammonium formate |
| HPLC | high performance liquid chromatography |
| HRGC | high resolution gas chromatography |
| HRMS | high resolution mass spectrometry |
| Hz | hertz |
| $IC_{90}$ | concentration required to inhibit virus replication by 90% |
| IR | infrared spectrometry |

| | |
|---|---|
| kbar | kilobar |
| kcal | kilocalorie(s) |
| $K_2CO_3$ | potassium carbonate |
| K*i* | inhibition constant |
| KO$^t$Bu | potassium *tert*-butoxide |
| LC | liquid chromatography |
| $LiAlH_4$ | lithium aluminum hydride |
| LiHMDS | lithium bis(trimethylsilyl)amide |
| LiOH | lithium hydroxide |
| *m*CPBA | *meta*-chloroperoxybenzoic acid |
| Me | methyl |
| MEM | (2-methoxyethoxy)methyl |
| M | moles per liter |
| MgO | magnesium oxide |
| MMP | matrix metalloproteinase |
| MsCl | methanesulfonyl chloride |
| MHz | megahertz |
| mL | milliliter(s) |
| mm | millimeter(s) |
| mmol | millimole(s) |
| mol | mole(s) |
| MOM | methoxymethyl |

| | |
|---|---|
| mp | melting point |
| MRSA | Methicillin-resistant *Staphylococcus aureus* |
| Ms | methanesulfonyl |
| MS | mass spectrometry |
| μL | microliter (s) |
| μω | microwave |
| NaCl | sodium chloride |
| $Na_2CO_3$ | sodium carbonate |
| NaH | sodium hydride |
| $NaHCO_3$ | sodium hydrogencarbonate |
| NaHMDS | sodium bis(trimethylsilyl)amide |
| $NaIO_4$ | sodium periodate |
| $NH_4OH$ | ammonium hydroxide |
| N | equivalents per liter (Normality) |
| nm | nanometer(s) |
| NMO | 4-methoxymorpholine *N*-oxide |
| NMR | nuclear magnetic resonance |
| NR | no reaction |
| Nuc | nucleophile |
| OACC | oligomeric alkyl cyclohexylcarbodiimide |
| OBAC | oligomeric bis-acid chloride |
| $OsO_4$ | osmium tetroxide |

| | |
|---|---|
| PBTD's | Pyrrolo[1, 2, 5]benzothiadizepines |
| $PCl_5$ | phosphorus pentachloride |
| Pd/C | palladium over charcoal |
| Tol | tolyl |
| $POCl_3$ | phosphoryl trichloride |
| $Pd(PPh_3)_4$ | tetrakis(triphenylphosphine)palladium |
| Ph | phenyl |
| $Ph_3P$ | triphenyl phosphine |
| PMB | *para*-methoxybenzyl |
| PMP | *para*-methoxyphenyl |
| ppm | parts per million |
| *i*-Pr | *iso*-propyl |
| PTAB | phenyltriethylammonium tribromide |
| PTSA | *para*-toluenesulfonic acid |
| Pyr. | pyridine |
| $R_f$ | retention factor |
| RCM | ring closing metathesis |
| ROMP | ring-opening metathesis polymerization |
| rt | room temperature |
| $RuCl_3$ | ruthenium chloride |
| SAMP | (*S*)-1-amino-2-methoxymethyl pyrrolidine |
| SAR | structure activity relationship |

| | |
|---|---|
| $S_N2$ | substitution nucleophilic bimolecular |
| TMSI | iodotrimethylsilane |
| $TXA_2$ | thromboxane $A_2$ |
| TBDPS | *t*-butyldiphenylsilyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TlOAc | acetylthallium(III) oxide |
| TMEDA | *N*, *N*, *N*', *N*′-tetramethylethylenediamine |
| TTMSS | tris(trimethylsilyl)silane |
| ZBG | zinc-binding group |

# Chapter 1

*Introduction: Synthetic Approaches to Sultams*

## 1.1 Sulfonamides: An Important Class of Medicinal Agents

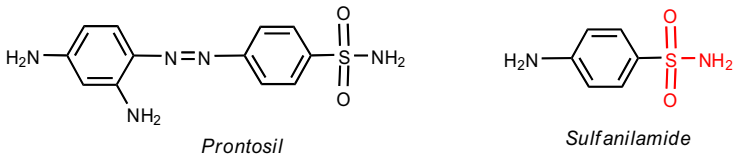
The purpose of this chapter is to review the literature for the preparation of sultams, which are the cyclic versions of sulfonamides. A brief and general introduction of the biological relevance of acyclic sulfonamides will be used to preface the topic.

### 1.1.1 Introduction

The sulfonamide moiety (-$SO_2$NHR) has become an important pharmacophore in medicinal chemistry; its origin, however, was the result of mere coincidence. The sulfonamide story began in the early 1900's, with the discovery of azo dyes, which were widely used in the production of fibers and textiles. Widespread use quickly prompted efforts to improve its properties. It was found that the introduction of the sulfonamide group (-$SO_2$NH-) gave dyes superior stability to light, greater water solubility during application, and greater fixation to fibers.[1] In 1933, a research group out of Germany, ignored the myth that bacterial infections could not be cured by drugs, and began testing the action of various dyes against streptococcal infections in mice. To their delight, the red dye prontosil was found to be an effective agent,[2] and further studies demonstrated its applicability in humans. Moreover, biological studies involving prontosil revealed that it acted as a pro-drug, which is metabolized in the body into the chemotherapeutically active sulfanilamide (Figure 1.1). This important discovery led to its clinical use for the treatment of bacterial infections. Subsequently, many compounds related to sulfanilamide have been synthesized and referred to as

sulfonamides. Currently, over 30 agents containing the sulfonamide moiety are under clinical use.

**Figure 1.1** *Chemical stucture of prontosil and sulfanilamide*




### 1.1.2 Biological Properties of Sulfonamides

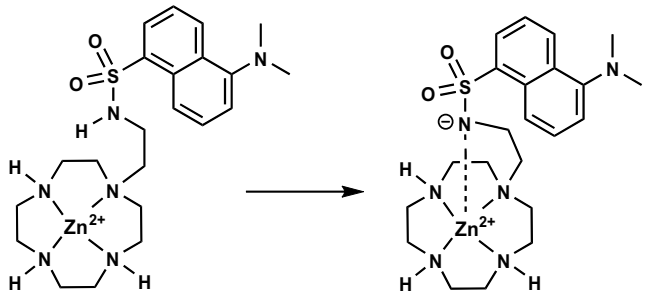
Due to its extensive biological profile, the sulfonamide moiety gained widespread use in medicinal chemistry. Chemical studies involving pKa measurements have revealed that this versatile entity is comparable to the carboxyl group and therefore, it has been utilized as a carboxyl isostere.[1] Studies have shown that sulfonamides serve as non-hydrolyzable amide surrogates, making them an ideal functional group in the synthesis of peptidomimetics.[3-7] It has been observed that the introduction of the sulfonamide moiety induces an increase in metabolic stability towards protease-catalyzed degradation of peptidosulfonamides.[8] For this reason, they have been used as transition-state analogues for amide bond hydrolysis, and have found applications as potential HIV protease inhibitors.[5, 6] Biological studies performed with histamine $H_3$ receptor antagonists revealed that the *in vitro* profiles of sulfonamides were superior to the corresponding amide analogs.[9-11]

Sulfonamides contain a high density of hydrogen bond donor and acceptor sites, which allow them to coordinate to amino acid residues located at the active sites of enzymes.[9] The sulfonamide moiety is also associated with increased bioavailability and increased water solubility relative to other polar groups

(e.g. amides).[9] These interesting properties have promoted the incorporation of the sulfonamide group into a growing number of compounds, many of which have demonstrated biological activity.

Sulfonamides have found extensive use as both carbonic anhydrase and matrix metalloproteinase inhibitors, which are a family of zinc containing enzymes implicated in a number of diseases such as arthritis and cancer.[12, 13] Studies performed on sulfonamides revealed that inhibition of these enzymes is brought about by their ability to mimic the tetrahedral transition state when binding to catalytic zinc ions located at the active site of the enzymes.[14-16] A model study that supports this coordination is presented in Figure 1.2.

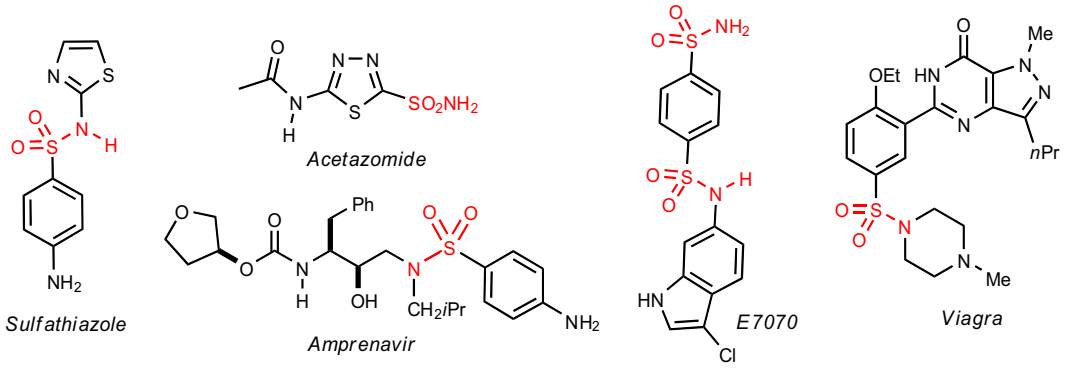
**Figure 1.2**




Sulfonamides have also shown antibacterial, diuretic, hypoglycemic, antithyroid, and most recently, antitumor activity.[17] Representative examples of biologically active sulfonamides are shown in Figure 1.3 including the antibacterial agent sulfathiazole,[18] the carbonic anhydrase inhibitor acetazolamide[19] which has been clinically used for more than 45 years, the anticancer agent E7070 which is currently in advanced clinical trials,[20] the HIV protease inhibitor amprenavir,[21] and

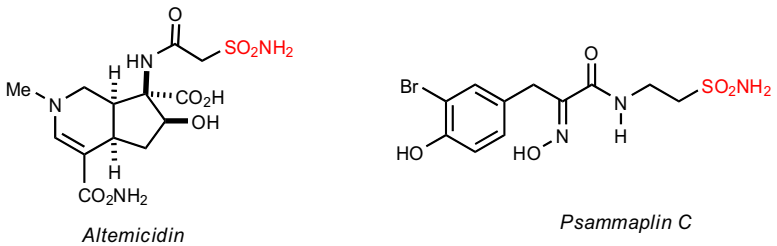
most recently Viagra (Sildenafil),[22] one of the most marketable drugs used for male erectile dysfunction.

**Figure 1.3** *Biologically active sulfonamides*




Only two examples of naturally occurring sulfonamides have been reported to date. Altemicidin,[23] isolated from the actinomycete strain *Streptomyces sioyaensis*, has shown tumor cell growth inhibition and psammaplin C,[24] isolated from the marine sponge *Psammaplysilla purpurea* (Figure 1.4). With the sparcity of naturally occurring sulfonamides, in conjunction with the attractive biological features of sulfonamide-containing compounds described so far, synthetic efforts towards the construction of compounds containing this functionality have been pursued. In many cases, their syntheses have been accomplished from readily available starting materials.

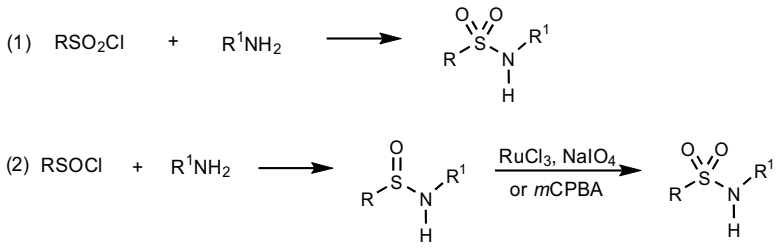
**Figure 1.4** *Naturally occurring sulfonamides*



### 1.1.3 Synthetic Approaches Toward Sulfonamides

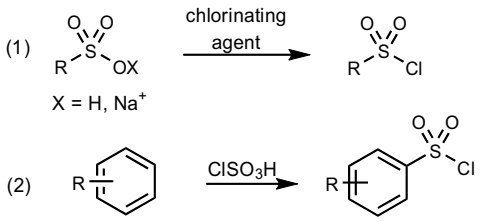
The usual way of preparing sulfonamides is by treatment of sulfonyl chlorides with ammonia or amines (Reaction 1, Scheme 1.1).[25] Treatment with ammonia gives primary sulfonamides, while primary and secondary amines give *N*-alkyl sulfonamides and *N,N*-dialkyl sulfonamides respectively. Alternatively, sulfonamides can be prepared from the corresponding sulfinyl chlorides, which are coupled with amines to form sulfinamides and then oxidized into sulfonamides (Reaction 2, Scheme 1.1).[26] In cases where the sulfonyl chloride is not commercially available it

**Scheme 1.1**




can be prepared from the respective sulfonic acid or their sodium salts using chlorinating agents such as $PCl_5$, $POCl_3$, $SOCl_2$, phosgene, or triphosgene (Reaction 1, Scheme 1.2).[26] Aromatic sulfonyl chlorides can be prepared by treatment of aromatic rings with chlorosulfuric acid ($ClSO_2OH$) (Reaction 2, Scheme 1.2).[27]

**Scheme 1.2**

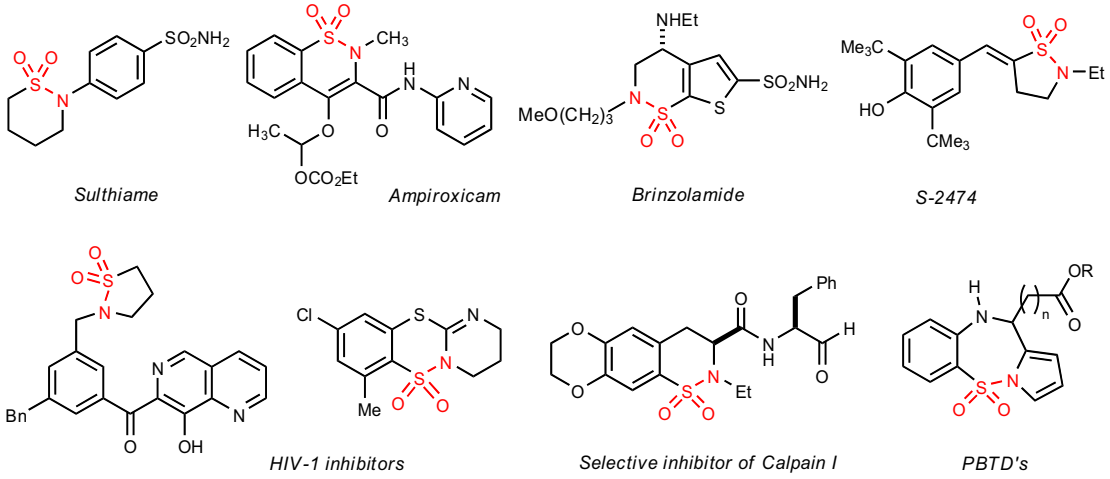


## 1.2 Sultams: Cyclic Sulfonamides

### 1.2.1 Biological Properties of Sultams

Cyclic sulfonamides (sultams) although not found in nature[28] have also found applications in drug development. Examples of biologically active sultams include the antiepileptic agent Sulthiame,[29] the antiinflamatory agent Ampiroxicam,[30] Brinzolamide[31, 32] for the treatment of glaucoma, S-2474,[33] a new anthiarthritic drug candidate that is now under clinical trials, HIV-1 inhibitors[34, 35] selective inhibitors of Calpain I,[36] and most recently PBTD's[37] which are a new class of candidates for the treatment of chronic myelogenous leukemia (CML) (Figure 1.5).

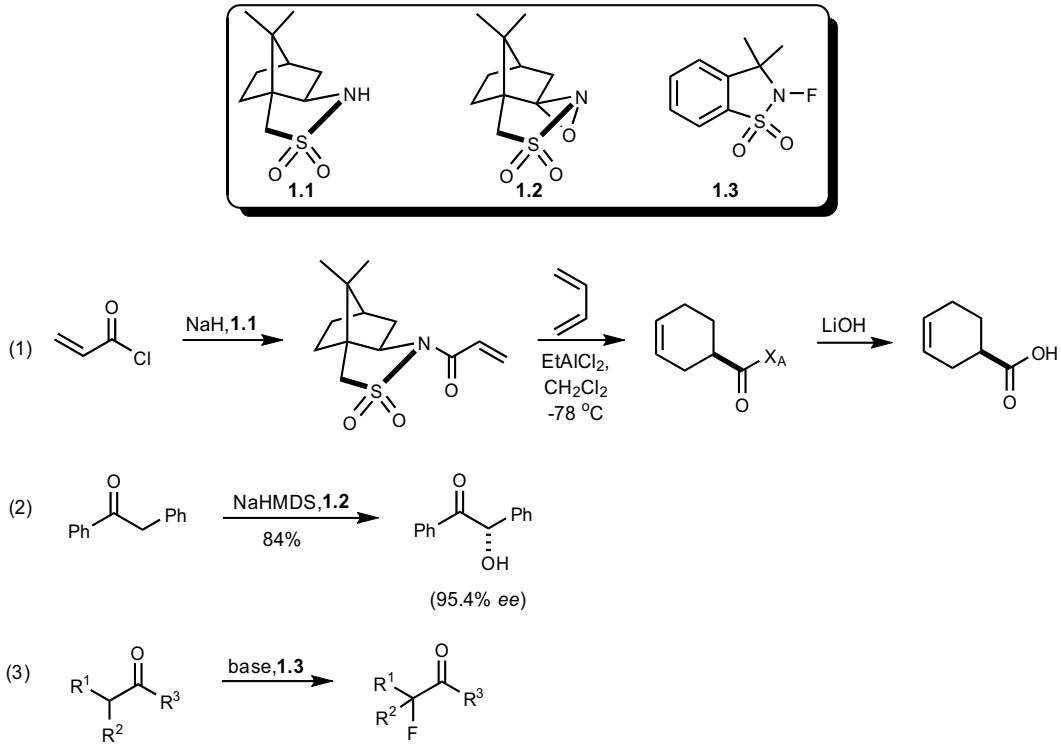
**Figure 1.5** *Biologically active sultams*




In addition to their medicinal value, sultams have been successfully used as chiral auxiliaries,[38, 39] reagents,[40-42] artificial sweeteners (i.e. saccharin),[43] and agricultural agents.[44] For example, the well known Oppolzer sultam **1.1** has been utilized in numerous asymmetric reactions (Reaction 1, Figure 1.6),[38, 39] sultam **1.2** has been used as a stereoselective oxidizing agent (Reaction 2, Figure 1.6)[42] and

sultam **1.3** has found application as an electrophilic fluorinating agent to provide monofluorinated ketones (Reaction 3, Figure 1.6). [40, 41] In agriculture, sultams have been used as herbicides.[44]

**Figure 1.6** *Sultams used as reagents in organic chemistry*




Despite the importance of sultams in medicinal and synthetic chemistry, methods to access these important compounds in an enantiomerically and diastereomerically pure fashion are still limited.

### 1.2.2 Synthesis of Sultams via Intramolecular Reactions

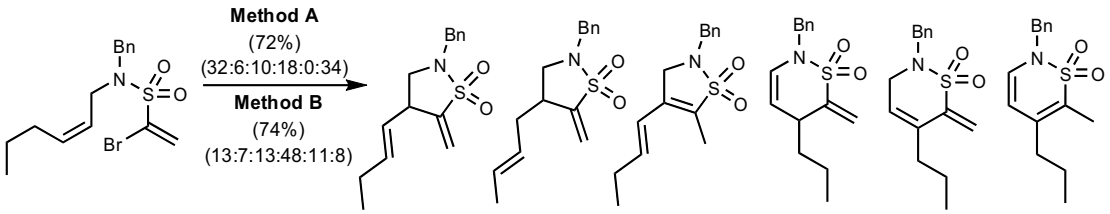
The following sections describe the most relevant methods that have been utilized to synthesize sultams, all of them based on intramolecular processess. The most common methods reported to date include the Heck reaction, Diels-Alder cycloaddition, 1,3-dipolar cycloaddition, base and acid-promoted cyclizations, radical

cyclizations, rhodium (Rh)-catalyzed cyclizations and ring-closing metathesis (RCM). Other more recently reported methods such as metal-catalyzed cyclizations involving gold (Au) and copper (Cu) will also be discussed. Although a variety of intramolecular cycloaddition reactions for the synthesis of sultams will be presented, considerable emphasis will be given to RCM cyclization, which is the key synthetic method used to access a variety of sulfur heterocycles (*S*-heterocycles) throughout this dissertation.

#### 1.2.2.1 Heck Reaction

A number of cyclization methods relying on C-C bond forming strategies have been reported for the synthesis of sultams. Of particular interest is the Heck reaction, where catalytic amounts of Pd, a suitable ligand and a base are utilized.[45, 46] In 2005, Metz and coworkers used the intramolecular Heck reaction for the synthesis of α-methylene-γ-sultams as potential cysteine protease inhibitors and demonstrated the use of these *S*-heterocycles as Michael acceptors with different sulfur nucleophiles.[47] Cyclic and acyclic allyl amines were used to synthesize the sulfonamide substrates applying the general method described before (Reaction 1, Scheme 1.1). Initially, cyclization of the sulfonamide substrates was performed under two different catalytic conditions: standard conditions (Method **A**: 5 mol % $Pd(PPh_3)_4$, $Et_3N$ (2 equiv.), MeCN, reflux, 2 h) and Method **B** (5 mol % $Pd(OAc)_2$, 11 mol % P(*o*-Tol)$_3$, $Bu_4NCl$ (2 equiv.), $Na_2CO_3$ (2 equiv.), MeCN, reflux, 1 h) which has been successfully utilized by Minnaard and coworkers for the synthesis of lactams (Scheme 1.3).[48]

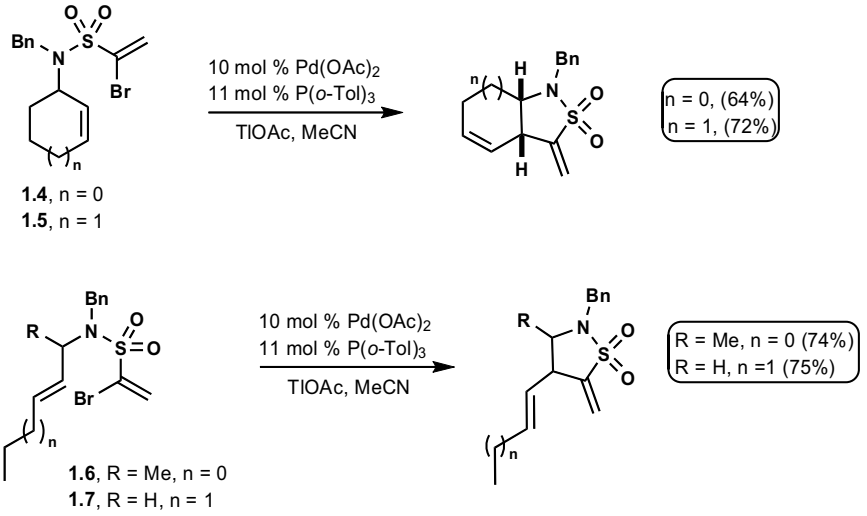
**Scheme 1.3**




Although the desired cyclized products were obtained under these reaction conditions, a mixture of byproducts resulting from double bond migration was observed (Scheme 1.3). To circumvent this problem, a variety of silver and thallium additives were investigated. Silver(I) additives have been documented to play a crucial role in the Heck reaction by increasing reaction rates, preventing deactivation of the catalyst, minimizing double bond isomerization of the products and enhancing enantioselectivity. [45] The silver salts act as effective halide scavengers, switching the Heck reaction from a neutral to a cationic pathway through dissociation of the halide. Thallium salts, although highly toxic, have also been used as halide scavengers in the Heck reaction through a similar pathway.[45] The optimized conditions for the cyclization of sulfonamides **1.4-1.7** (Scheme 1.4) were obtained in the presence of 10 mol % $Pd(OAc)_2$ as the catalyst, 11 mol % of P(*o*-Tol)$_3$ as the ligand, and 2 equiv. of thallium acetate (TlOAc) as an additive in refluxing MeCN for 3-5 h. The resulting sultams were obtained in good yields (64-75%) as the only products (Scheme 1.4).

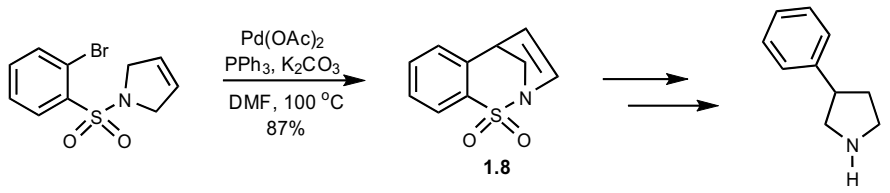
In contrast to *N*-benzyl sulfonamides **1.4-1.7** sulfonamides containing a free N-H bond failed to cyclize under the optimized reaction conditions, even under prolonged reaction times (5 days in refluxing acetonitrile).

**Scheme 1.4**



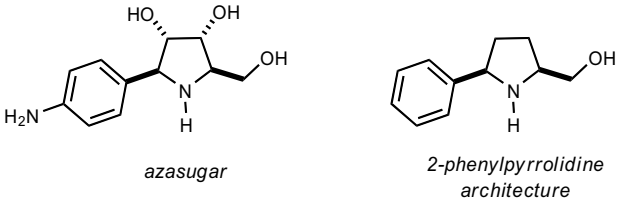

While Metz and coworkers were able to use the Heck reaction for the synthesis of monocyclic and bicyclic sultams, Evans and coworkers applied the same synthetic strategy towards the synthesis of tricyclic sultams, which were later converted to pyrrolidines and piperidines.[49] Although using the identical palladium catalyst as Metz and coworkers [$Pd(OAc)_2$], no additive seemed to be necessary to perform the reaction. Treatment of the aromatic sulfonamide in Scheme 1.5 with 10 mol % $Pd(OAc)_2$ in the presence of 20 mol % $PPh_3$, $K_2CO_3$ (2 equiv.) and DMF at 110 °C for 15 h afforded tricyclic sultam **1.8** in very good yield (87%).

**Scheme 1.5**



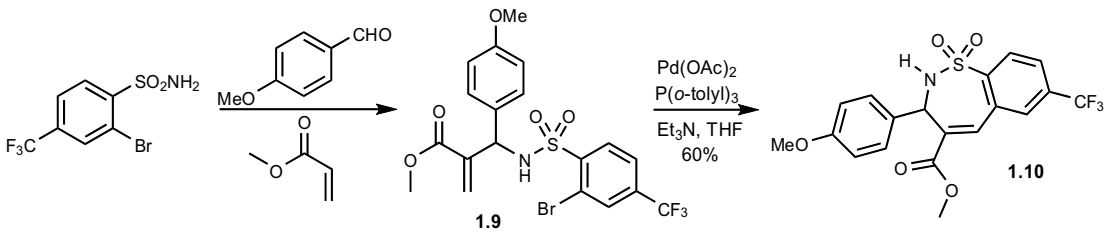
However, in a number of cases, the product arising from double bond isomerization was obtained. Further reduction of sultam **1.8** led to the synthesis of aryl-substituted pyrrolidines. This sequence was adapted to the synthesis of the enantiomerically pure 2-phenylpyrrolidine structures present in many natural and nonnatural aza sugars (Figure 1.7).[50]

**Figure 1.7**




Analogous to the work reported by Metz, Vasudevan and coworkers utilized a Heck coupling reaction for the synthesis of bicyclic aromatic sultams such as **1.10**[51] (Scheme 1.6). Sulfonamide **1.9**, generated via an aza-Baylis-Hillman reaction with 2-bromo-4-(trifluoromethyl)benzenesulfonamide, 4-methoxybenzaldehyde and methyl acrylate, underwent intramolecular Heck coupling with 5 mol % $Pd(OAc)_2$, 2 mol % P(*o*-tolyl)$_3$, and $Et_3N$ in THF at 160 °C for 1 h to afford the conformationally strained bicyclic sultam **1.10** in moderate yield (60%) (Scheme 1.6). Although this procedure afforded the desired bicyclic sultam, high temperatures were required.

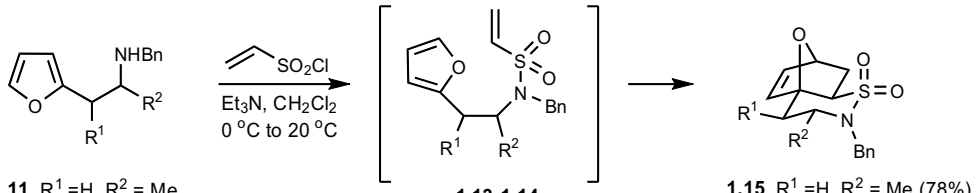
**Scheme 1.6**



### 1.2.2.2 Diels-Alder Cyclization

The Diels-Alder reaction has been fairly utilized for the synthesis of bicyclic sultams. In 1996, Metz and coworkers reported the synthesis of δ- and γ-sultams via the Diels-Alder cycloaddition reaction starting from *N*-benzylaminoalkyl substituted furans.[52] Benzylamines **1.11** and **1.12** were prepared from their respective racemic alcohols by nucleophilic displacement of their tosylates with benzylamine. These amines were then treated with vinylsulfonyl chloride, forming the sulfonamide intermediates **1.13** and **1.14** that readily underwent the cycloaddition reaction to provide bicyclic sultams **1.15** and **1.16** in high yields as a mixture of diastereomers (Scheme 1.7).

**Scheme 1.7**



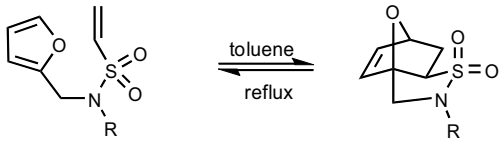

**1.11**, $R^1$ =H, $R^2$ = Me
**1.12**, $R^1$ =Me, $R^2$ = H

**1.13-1.14**

**1.15**, $R^1$ =H, $R^2$ = Me (78%)
isomer (94:6)
**1.16**, $R^1$ =H, $R^2$ = Me (92%)
isomer (92:8)

The cyclization reaction was also performed with sulfonamides **1.17-1.19**, featuring a three atom tether connecting the furan and dienophile moieties (Scheme 1.8). In contrast to vinyl sulfonamides **1.13** and **1.14**, (Scheme 1.7) sulfonamides **1.17-1.19** did not undergo cyclization during their preparation. Although no ring closure was observed for **1.17** (R=H) in refluxing toluene, an equilibrium mixture of **1.18-1.21** and **1.19-1.22** was attained at this elevated temperature, with the best conversion achieved for **1.22** (R = Bn, 91% yield).

**Scheme 1.8**

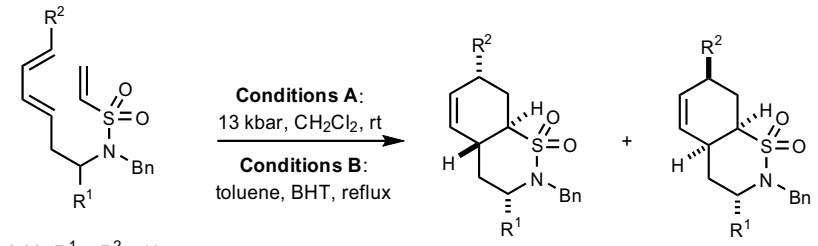



**1.17**, R = H
**1.18**, R = Me
**1.19**, R = Bn

**1.20**, 0%
**1.21**, 29%
**1.22**, 91%

The application of high pressure (13 kbar in $CH_2Cl_2$ at room temperature) was also examined. These reaction conditions were applied to the Diels-Alder cyclization of sulfonamides **1.23** and **1.24** and the results compared to the reaction performed under refluxing toluene (Table 1.1).[53]

**Table 1.1** *Intramolecular Diels-Alder reaction of sulfonamides **1.23** and **1.24***



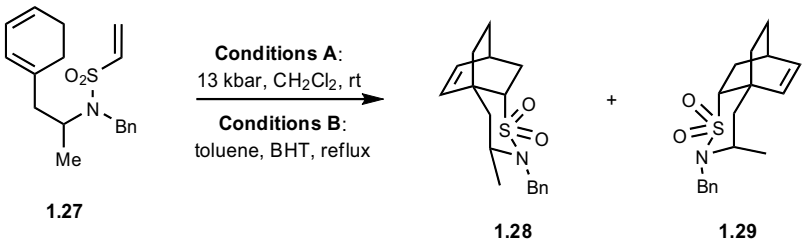

**1.23**, $R^1 = R^2 = H$
**1.24**, $R^1 = R^2 = Me$

**1.25** + **1.26**

| Reaction Conditions | $R^1$, $R^2$ | **1.25:1.26** ratio | % Yield |
|---|---|---|---|
| A | H | 1.0 : 1.6 | 79 |
| B | H | 1.0 : 1.0 | 76 |
| A | Me | 1.0 : 1.9 | 81 |
| B | Me | 1.6 : 1.0 | 61 |

The radical scavenger BHT proved beneficial for the reaction performed under refluxing toluene by suppressing side reactions at elevated temperatures. From the results shown in table 1.1, it is evident that the yields of the cyclization products improved at higher pressures. These conditions also favored the formation of the *endo* product, whereas at atmospheric pressure there is no *endo*/*exo* discrimination. When the same reaction conditions were applied to cyclic 1,3-diene **1.27** (Table 1.2), the adduct **1.28** is formed preferentially over **1.29** at atmospheric pressure and is enhanced at higher pressures.

**Table 1.2** *Results of the Diels-Alder cycloaddition of sulfonamide **1.27***



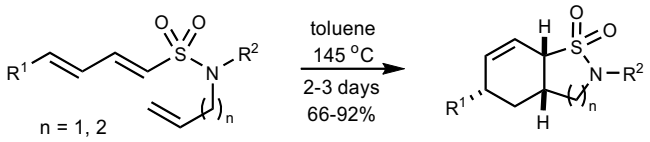

**1.27** **1.28** **1.29**

| Reaction Conditions | **1.28 : 1.29** ratio | % yield |
|---|---|---|
| A | 30.3 : 1.0 | 93 |
| B | 9.3 : 1.0 | 77 |

The same study was reported for the synthesis of enantiopure 5- and 6-membered ring sultams containing a chiral auxiliary attached to the nitrogen atom.[54] In this case, the cycloaddition performed at higher pressures was associated with a higher asymmetric induction and higher overall yields than the reaction performed at ambient pressure. These results suggest that higher pressure conditions are necessary to improve the yields and selectivities of the cyclized products.

In 2001, Wright and coworkers applied the thermal Diels-Alder reaction to the synthesis of bicyclic sultam histamine $H_3$ receptor antagonists.[55] The trienes utilized for the intramolecular Diels-Alder reaction were obtained from condensation of *N*-Boc-methanesulfonamide with different aldehydes followed by alkylation. The cyclization reactions were performed at 145 °C in toluene in a sealed tube for two to three days (Scheme 1.9). Lower temperatures, such as toluene at reflux were not successful. Even though prolonged reaction times were required, the cyclized adducts were obtained in good to excellent yields.

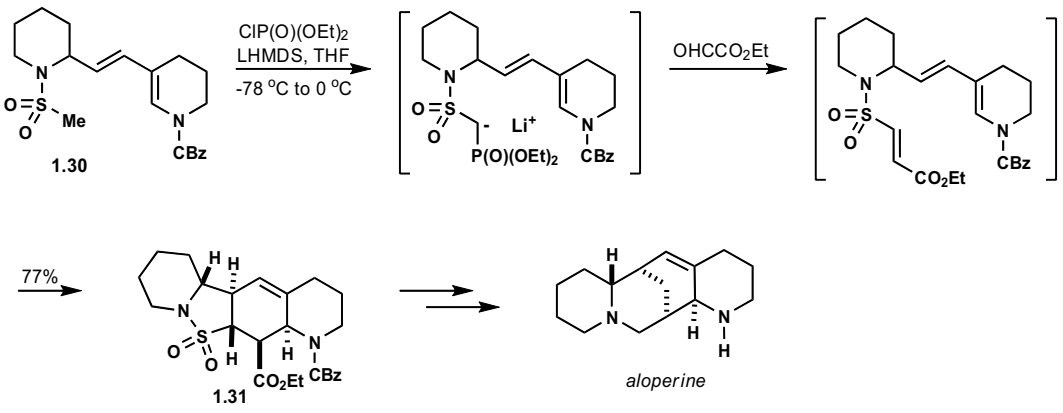
**Scheme 1.9**




Sultams have also found use as tethers for the synthesis of natural products. In 1999, Overman and coworkers utilized tetracyclic sultam **1.31** (Scheme 1.10), generated via an intramolecular Diels-Alder reaction, during the total synthesis of the natural product (+)-aloperine.[56] Deprotonation of methanesulfonamide **1.30** with LHMDS in the presence of diethyl chlorophosphate, followed by the in situ addition of ethyl glycoxylate, readily generated sultam **1.31** in a 3.4:1 ratio of cycloadducts (Scheme 1.10). The $SO_2$ group was intended to be removed from the cycloadducts under reductive conditions, proving that this entity could also serve as a removable tether in organic synthesis. Many of the attempted reductive conditions failed to cleave the $SO_2$ tether either at the N-S or C-S bonds. Only one of the reductive conditions tried worked (sodium or lithium in refluxing ammonia), albeit providing

the desired product in minimal quantities. These results contrast the observations made by Evans and coworkers where they successfully removed the $SO_2$ moiety under metal reductive conditions en routes to aryl substituted cyclic amines.[49] Due to the failure of this synthetic route, a different tether approach was used to synthesize (+)-aloperine.

**Scheme 1.10**

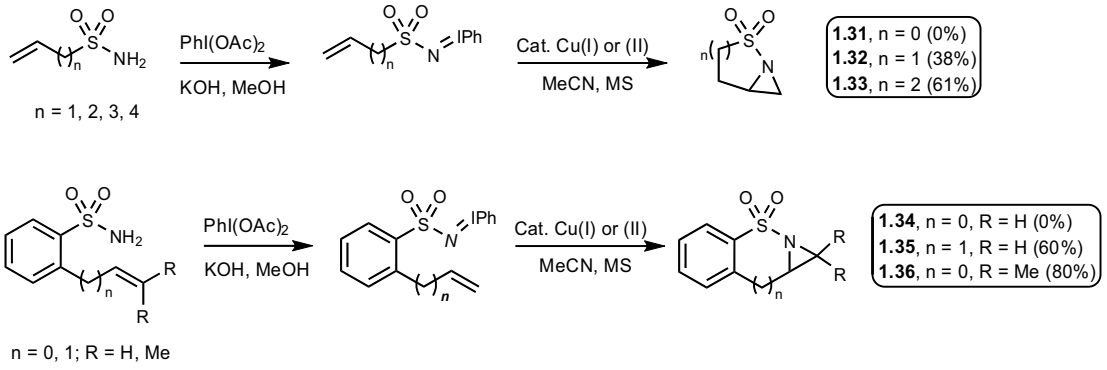



### 1.2.2.3 Copper-Catalyzed Cyclizations

In 2000, Dodd and coworkers reported a new strategy for the synthesis of various sultams based on intramolecular copper catalyzed nitrene delivery.[57] Their study showed the first intramolecular copper-catalyzed aziridination of primary sulfonamides via an iminoiodinane intermediate. Both linear and aromatic sulfonamides were utilized as starting materials. The linear sulfonamides were synthesized in three steps via published protocols starting from the respective alkyl bromides. The benzenesulfonamides used were synthesized via a two-step protocol involving an *ortho*-metalation step followed by acidic cleavage of the sulfonamide *N-t*-butyl group. A variety of aliphatic and aromatic sulfonamides were treated with

iodobenzene diacetate [$PhI(OAc)_2$] and potassium hydroxide in methanol, affording the respective iminoiodinane intermediates, which upon purification via simple extraction were treated with catalytic copper triflate in MeCN to afford the corresponding sulfonamide aziridines **1.31-1.36** in moderate to good yields (Scheme 1.11).

**Scheme 1.11**

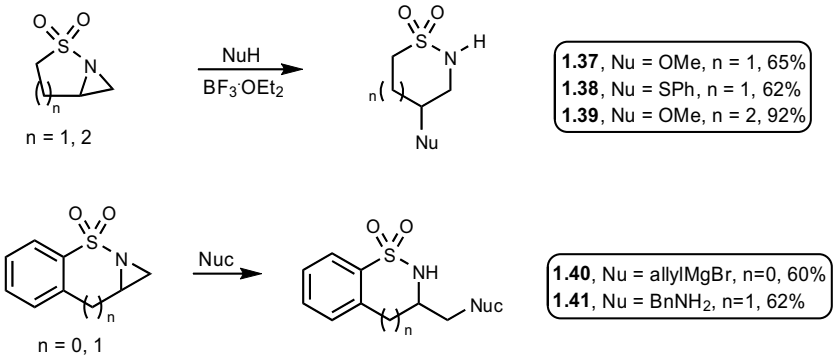



As expected, the cyclization of the allyl iminoiodinane intermediate (n = 1) failed to form the strained 4-membered ring bicyclic sultam **1.31**, while the cyclization of the 5-hexene iminoiodinane intermediate (n = 4) gave exclusively the allylic insertion product instead of the aziridine. These copper-catalyzed C-H insertion products have been rarely observed in analogous intramolecular aziridination reactions. In the case of the benzene sulfonamides, the vinyl iminoiodinane intermediate (n = 0) failed to give the respective aziridine **1.34** under the same reaction conditions. The desired aziridine was only observed via bromine-catalyzed aziridination in the presence of phenyltrimethylammonium tribromide (PTAB). For more sterically hindered benzene sulfonamides (R = Me), the desired

aziridine **1.36** was achieved in good yield (80%). Similar yields for the cyclization step were obtained when the reaction was performed using the *N*-chloramine salts of the respective linear and benzene sulfonamides, followed by addition of catalytic quantities of PTAB.[58]

Ring opening of various aziridines was accomplished in the presence of different nucleophiles such as alcohols, thiols, Grignard reagents and benzylic amines to afford five-, six-, and seven-membered ring functionalized sultams in good to excellent yields (Scheme 1.12). Non-aromatic aziridines led to exclusive opening at the more substituted carbon to provide sultams **1.37-1.39** in good to excellent yields (62-92%), while aromatic aziridines reacted at the less substituted carbon to afford functionalized sultams **1.40** and **1.41** in good yields (60% and 62%, respectively).

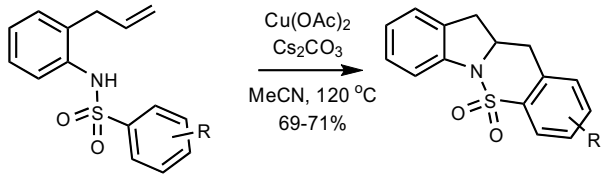
**Scheme 1.12**




The cyclization of sulfonamides catalyzed by copper(II) acetate has also been reported. In 2004, the Chemler group reported the synthesis of tetracyclic sultams via oxidative cyclization promoted by copper(II) acetate in the presence of base (Scheme 1.13).[59] The best reaction conditions for the oxidative cyclization reactions were realized at elevated temperatures (120 °C) in a pressure tube with polar solvents such

as MeCN and DMF. The resulting aromatic sultams were obtained in relatively good yields (69-71%).

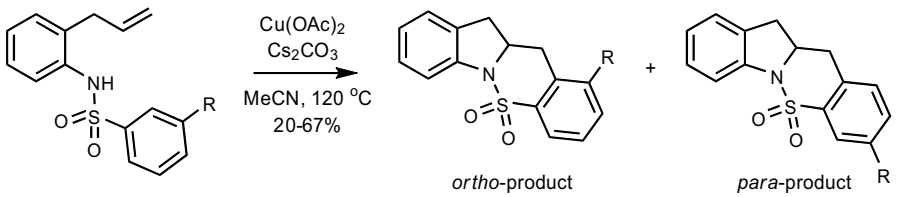
**Scheme 1.13**




R = Me, OMe, $NO_2$, Br, Cl

A variety of arylsulfonyl-*o*-allylalanines bearing different *para*- and *meta*-substituents in the sulfonyl aromatic ring were studied to determine the scope of the reaction. It was found that the yields and selectivities of the products obtained were dependent on the substituent present in the aromatic ring. With electron donating groups (Me, OMe) at the *para*-position of the sulfonamide group, the reaction proceeded in moderate to good yields (43-73%), leading to the exclusive formation of the *para*-tetracyclic sultam (*para*-product). However, *meta*-substitution led to a mixture of regioisomeric products as shown in Scheme 1.14. The same results were observed for *meta*-substituted chlorine substrates.

**Scheme 1.14**




R = Me, OMe, Cl

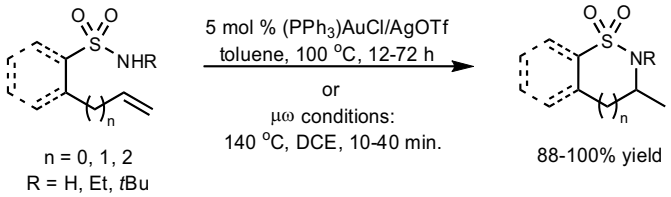
Two interesting results were obtained during the course of their study. When *meta*-substituted nitrosulfonamide was used, the product obtained was exclusively the *ortho* product. With *para*-substituted bromosulfonamide the *ortho*-cyclized product

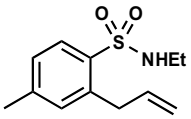
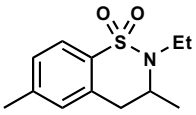
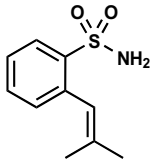
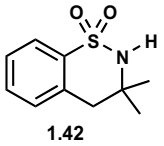
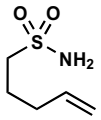
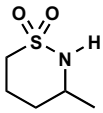
obtained lacked the bromide functionality. All these cases provided exclusively the *ortho* product, albeit low yields (~25%) except in one case, when addition of DMSO dramatically increased the yield to 54%. The rate-enhancing effects of DMSO in Pd(II)-catalyzed reactions appears to be associated with its palladium-coordination activity. Having both soft (S) and hard (O) ligand donor atoms seems to facilitate the reduction-oxidation cycling between Pd(II) and Pd(0) in this type of reactions.[60]

#### 1.2.2.4 Gold-Catalyzed Cyclization

In **e**arly 2006, the first example for the synthesis of sultams catalyzed by gold(I) phosphine complexes was reported.[61] This study showed the intramolecular amination of unactivated alkenes under both thermal conditions and microwave irradiation. The best reaction conditions were obtained using 5 mol % of $(PPh_3)AuCl/AgOTf$ in toluene at 60-100 °C for 12-72 h (Table 1.3). A variety of sulfonamides were subjected to these reaction conditions providing the respective sultams in excellent yields (88-100%). The reaction was successful even when steric hindrance was present at the double bond as shown in sultam **1.42** (Table 1.3). To shorten the reaction times, all the reactions were performed under microwave irradiation at 140 °C in DCE and the results compared to the reactions performed under thermal conditions. A considerable reduction in reaction time (less than 1 h) was observed for these new reaction conditions (Table 1.3). This new methodology seems promising for further study towards more elaborate sultams and its application towards the synthesis of enantiopure sultams.

**Table 1.3** *Gold(I)-catalyzed cyclization under thermal and microwave conditions*



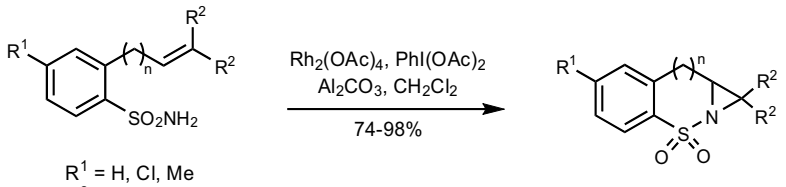

| Substrate | Product | Thermal Cond. Time (h) | % Yield | μω Cond. Time (min.) | % Yield |
|---|---|---|---|---|---|
|  |  | 24 | 95 | 40 | 90 |
|  |  **1.42** | 12 | 99 | 10 | 100 |
|  |  | 72 | 95 | 40 | 95 |

### 1.2.2.5 Rhodium-Catalyzed Cyclizations

Inspired by the work of DuBois and Breslow involving intramolecular amidation reactions of saturated C-H bonds catalyzed by rhodium (II) dimers and recent work by Dodd[57] showing copper-catalyzed aziridination of sulfonamides (see Scheme 1.11, vide supra), Che and coworkers studied the intramolecular aziridation of sulfonamides catalyzed by rhodium (II) dimers such as $Rh_2(OAc)_4$ to provide the

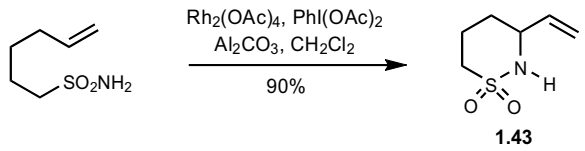
corresponding aziridines in excellent yields[62] (Scheme 1.15). From previous work in their laboratories it was observed that a combination of $PhI(OAc)_2$ and primary sulfonamides ($ArSO_2NH_2$) could be used as the nitrogen source in intramolecular amidation reactions. Further studies addressed to both aromatic and aliphatic sulfonamides revealed that the intramolecular aziridination was also possible with $PhI(OAc)_2$ as the oxidant when catalyzed by $Rh_2(OAc)_4$. The best results for the intramolecular aziridination were obtained using $Rh_2(OAc)_4$ (0.02 equiv.), $PhI(OAc)_2$ (1.5 equiv.) and $Al_2CO_3$ (2.5 equiv.) in refluxing $CH_2Cl_2$ for 3 h. The generality of this protocol was demonstrated using a variety of unsaturated sulfonamides to provide the aziridine products in excellent yields and conversions (Scheme 1.15).

**Scheme 1.15**




In a single case, the aziridine was not detected when aliphatic sulfonamides were used. Instead, vinylic sultam **1.43**, arising from C-H bond insertion, was isolated (Scheme 1.16). Dodd and coworkers have reported similar results.[57]

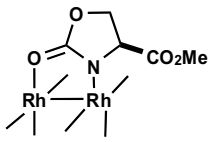
**Scheme 1.16**




**1.43**

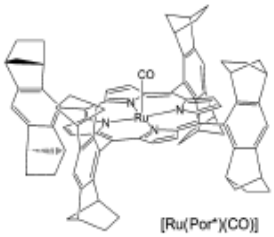
The enantioselective synthesis of aromatic sultams described in Scheme 1.15 is an area of great interest. Screening of a variety of chiral rhodium catalysts revealed that **1.44** gave the best enentioselectivities with values up to 76% *ee* in good to excellent yields (Figure 1.8).[63] Replacing the catalyst with the more robust ruthenium porphyrine complex **1.45** resulted in a dramatic drop in enantioselectivity for the best case presented (65% yield and 9% ee).[64] Similar attempts were performed by Fruit and coworkers for the synthesis of both aliphatic and aromatic amines catalyzed by chiral dirhodium complexes in the presence of $PhI(OAc)_2$ and MgO.[65] However, these reaction conditions provided the chiral sultams with selectivities up to 66% *ee* when using **1.46** as catalyst.

**Figure 1.8**

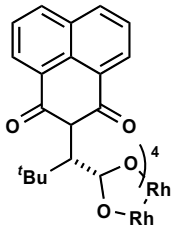



$Rh_2(4S\text{-MEOX})_4$

**1.44**




**1.45**




$[Rh_2\{(S)\text{-nttl}\}_4]$

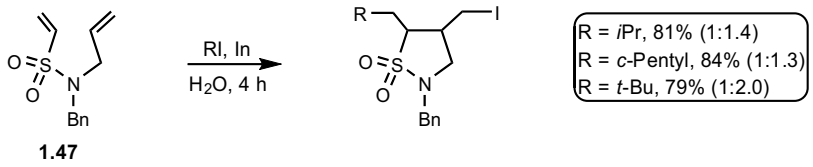
**1.46**

### 1.2.2.6 Radical Cyclizations

Free radical cyclization reactions have been employed for the construction of C-C bonds and have found application towards the synthesis of sultams. The cyclization of ally vinyl sulfonamides has been achieved using indium as a single-electron transfer radical initiator.[66] When sulfonamide **1.47** was subjected to the radical cyclization reaction using indium (2 equiv.) and various alkyl halides in water,

the desired sultams were obtained in good yields without the formation of byproducts, although a *cis*/*trans* mixture was observed (Scheme 1.17).

**Scheme 1.17**

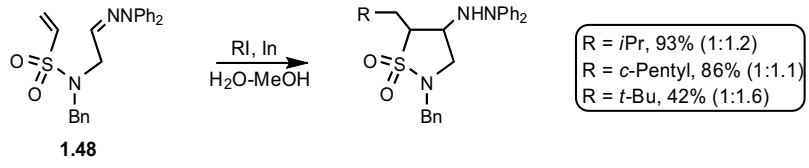



**1.47**

It was found that indium is an excellent radical initiator in aqueous solvents, providing the best yields (84%) in only 4 h. In biphasic systems ($H_2O$-$CH_2Cl_2$) the yields dropped substantially (42%) and the reaction required longer times (48 h).

The same reaction was applicable to sulfonamides bearing an imine terminal, such as hydrazone **1.48** (Scheme 1.18). In this particular case, a large amount of indium (10 equiv.) was required for the success of the reaction, providing the respective hydrazine sultams in good to excellent yields (42-93%) as a *cis*/*trans* mixture. Even in biphasic solvent systems ($H_2O$-$CH_2Cl_2$), the reaction proved successful with this substrate, providing isopropyl sultam (R = *i*Pr) in 93% yield.

**Scheme 1.18**

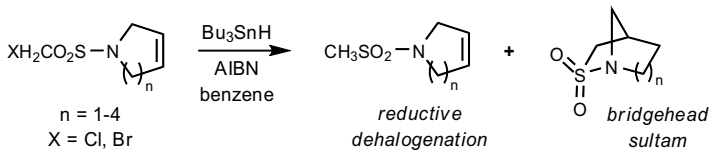


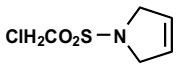
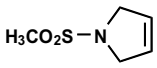
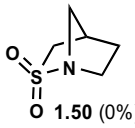
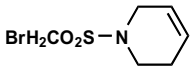
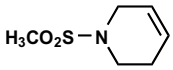
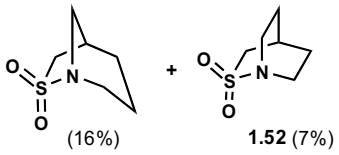
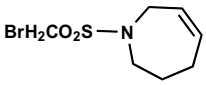
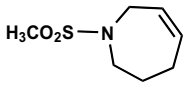
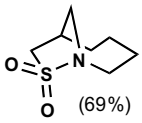
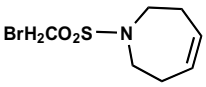
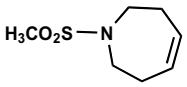
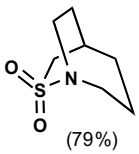
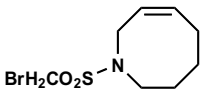
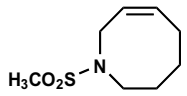
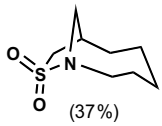

**1.48**

In 1999, the first example of the synthesis of bridgehead bicyclic sultams was reported by Paquette and coworkers.[67] A variety of α-halomethylsulfonamides were heated with tri-*n*-butyltin hydride ($Bu_3SnH$, 1.2 equiv.) and AIBN (0.07 equiv.) in

benzene to provide a mixture of products, one arising from simple reductive dehalogenation, and the second one being the desired bridgehead sultam (Table 1.4).

**Table 1.4** *Intramolecular radical cyclization of various α-halomethylsulfonamides*



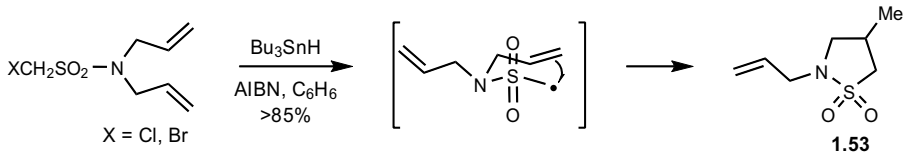

| Sulfonamide | Reduction product (% yield) | Bridgehead sultam (% yield) |
|---|---|---|
|  **1.49** |  (74%) |  **1.50** (0%) |
|  **1.51** |  (47%) |  (16%) + **1.52** (7%) |
|  |  (12%) |  (69%) |
|  |  (10%) |  (79%) |
|  |  (49%) |  (37%) |

Only in the case of sulfonamide **1.49**, the desired cyclization product **1.50** was not achieved, presumably due to the increased ring strain encountered in the formation of

this bridgehead sultam. In the case of sulfonamide **1.51**, the formation of bridgehead sultam **1.52** resulted from competing 6-*endo* C-C bond formation. Table 1.4 shows the products and yields obtained under these reaction conditions.

That same year (1999) Paquette and coworkers realized the intramolecular cyclization of radicals generated from α-halomethylsulfonamides to synthesize sultams.[68] Although it has been documented that α-sulfonyl radicals can be difficult to generate[69] and lack stability,[70, 71] various α-halomethylsulfonamides cyclized to sultam **1.53** (Scheme 1.19) via generation of the respective α-sulfonamidyl radical when reacted with $Bu_3SnH$, (1.1-3.0 equiv.) and AIBN (0.07-0.47 equiv.) in benzene in more than 85% yield.

**Scheme 1.19**

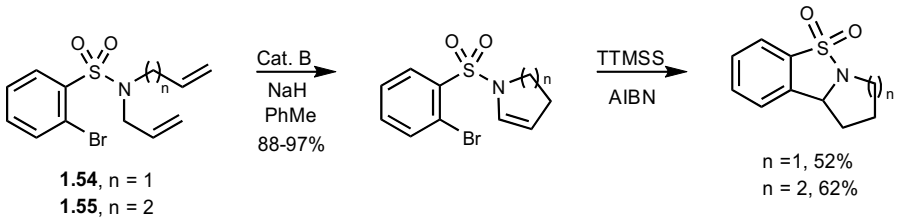



A variety of α-halomethylsulfonamide homologs were also subjected to the radical cyclization reaction. Depending on the double bond chain length, competition pathways between the respective *endo* or *exo* cyclization modes gave rise to a mixture of sultams.

A cascade RCM/isomerization reaction followed by a sequential radical cyclization has been implemented by Piva and coworkers for the synthesis of tricyclic sultams.[72] Sulfonamides **1.54** and **1.55** were subjected to the RCM reaction using Grubbs first generation catalyst (Cat. **B**), followed by double bond migration with sodium hydride (NaH), giving the corresponding sulfonamides in excellent yields

(Scheme 1.20). These new products were subjected to the radical cyclization reaction in the presence of tris(trimethylsilyl)silane (TTMSS) and AIBN to form the respective tricyclic sultams in good yields (52-62%).

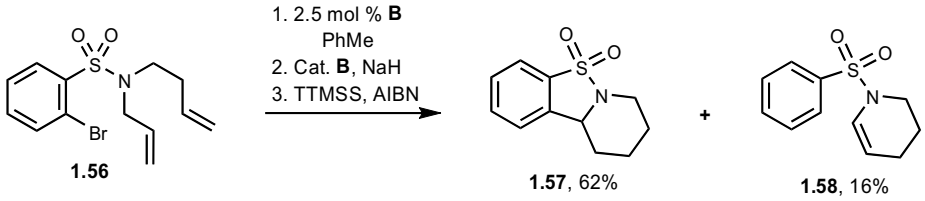
**Scheme 1.20**




**1.54**, n = 1
**1.55**, n = 2

With these results in hand the authors performed the same reaction sequence in a one-pot procedure with sulfonamide **1.56** (Scheme 1.21). Although a mixture of sultam **1.57** and sulfonamide **1.58** were obtained, the one-pot procedure proved useful for the synthesis of tricyclic sultams providing the desired compound **1.57** with yields comparable to the stepwise protocol.

**Scheme 1.21**




**1.56**

**1.57**, 62%

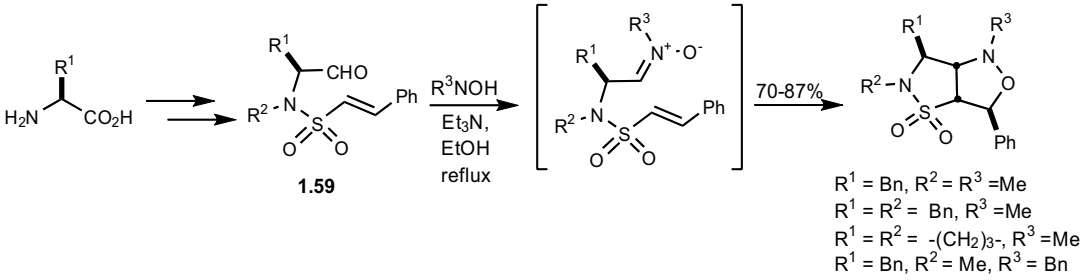
**1.58**, 16%

Some examples of radical cyclization reactions via irradiation of sulfonamides with $PhI(OAc)_2$ and $I_2$ in the presence of a tungsten lamp have also been reported.[73, 74] This synthetic pathway has been useful for the synthesis of benzosultams[73] and saccharine derivatives[74] in moderate to excellent yields.

### 1.2.2.7 1,3-Dipolar Cycloadditions

Interested in the biological profile offered by sultams, Chiacchio and coworkers pursued the synthesis of annulated sultams via 1,3-dipolar cycloaddition reactions.[75] The synthesis of the cyclization precursor was attained from *L*-amino acids via a three-step sequence. Treatment of aldehyde **1.59** with *N*-substituted hydroxylamines ($R^3$ = Me, Bn) under basic conditions afforded the nitrone intermediate which readily underwent a 1,3-dipolar cycloaddition to form the respective bicyclic sultams in good yields and complete diatereoselectivity based on NMR analysis of the crude products (Scheme 1.22). The excellent diastereoselectivity of the cycloaddition step was shown to be dependent on the stereocenter at the α-position of the sulfonamide ($R^1$).

**Scheme 1.22**



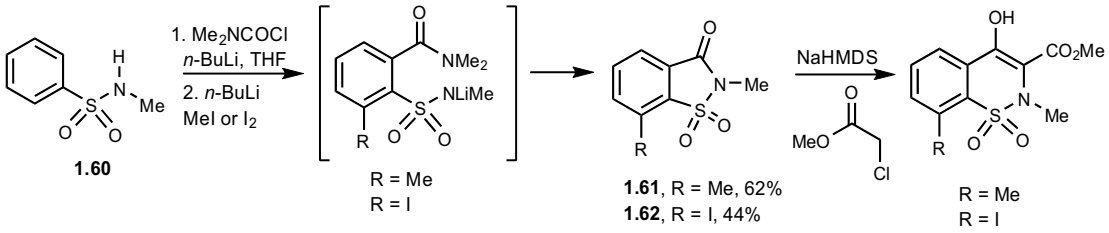

In addition to *N*-substituted hydroxylamines, primary amines and hydrazones were used in the cycloaddition reaction, providing the respective bicyclic sultams in good yields.

### 1.2.2.8 Base-Promoted Cyclizations

One of the most popular methods to synthesize sultams has been base-promoted cyclization. An interesting example published by Proudfoot and coworkers

makes use of substituted saccharins as precursors, followed by ring expansion.[76] The synthesis of the saccharide derivatives **1.61** and **1.62** began with the introduction of a dimethylcarbamoyl group in sulfonamide **1.60** (Scheme 1.23). Under basic conditions *ortho*-lithiation of sulfonamide **1.60** followed by addition of iodomethane or iodine provided the methyl or iodo derivatives which subsequently closed under the basic conditions to afford the saccharine derivatives **1.61** and **1.62** in acceptable yields (62% and 44% respectively) after workup. Saccharins **1.61** and **1.62** were then transformed into oxicams by ring expansion with methyl chloroacetate and NaHMDS.

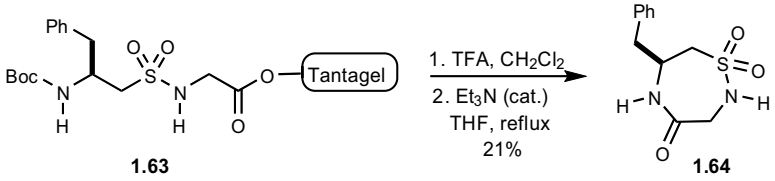
**Scheme 1.23**




In 1996, Liskamp and coworkers explored a solid-phase approach towards the synthesis of peptidosulfonamides.[77] Initial attempts using the Merrifield resin as the solid support proved problematic. To circumvent these problems, the resin was switched to Tantagel, since better solvation is possible and therefore, close to homogeneous reaction conditions can be obtained. The resin of choice was introduced in the early steps of the synthesis via coupling with an amino acid. Further reaction with an alkyl sulfinyl chloride followed by oxidation provided sulfonamide **1.63**. Boc-deprotection of sulfonamide **1.63** with TFA in DCM, followed by washing with $Et_3N$ (Scheme 1.24), and heating the reaction mixture for 5 days in the presence of $Et_3N$ afforded, upon removal of the resin by filtration, the 7-

membered ring sultam **1.64** in only 21% yield. The cyclization step serves a dual role in this reaction by simultaneously generating the sultam while cleaving the resin. Even though this reaction provides a facile route to cyclic peptidosulfonamides using a solid support approach, room for optimization is evidenced by the low reaction yields.

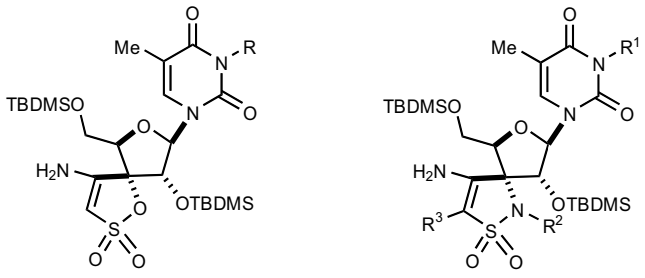
**Scheme 1.24**




**1.63** **1.64**

In 2004 Postel and coworkers performed a study for the base-promoted cyclization of a series of enantiomerically pure spiro (4-amino-5-*H*-2,3-dihydroisothiazole-1,1-dioxide) ring systems on sugar templates with the goal of accessing a novel range of aza analogs of TSAO nucleosides (ATSAOs, Figure 1.9).[78]

**Figure 1.9**



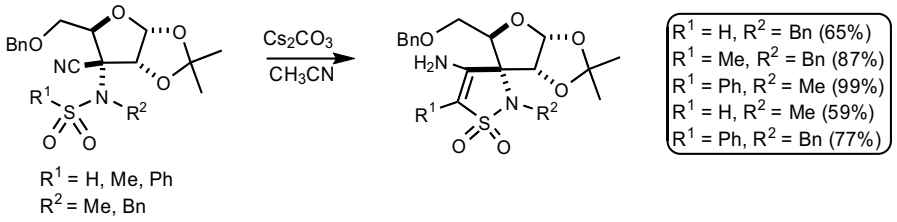

**TSAO-T** (R = H)
**TSAO-*m*$^3$T** (R = Me)

**ATSAO-T derivatives**

These carbanion-mediated cyclizations were investigated in the presence of different bases ($K_2CO_3$, $Cs_2CO_3$, *n*-BuLi and LDA). It was observed that the success of the reaction depended upon the compatibility of the base with the substituents

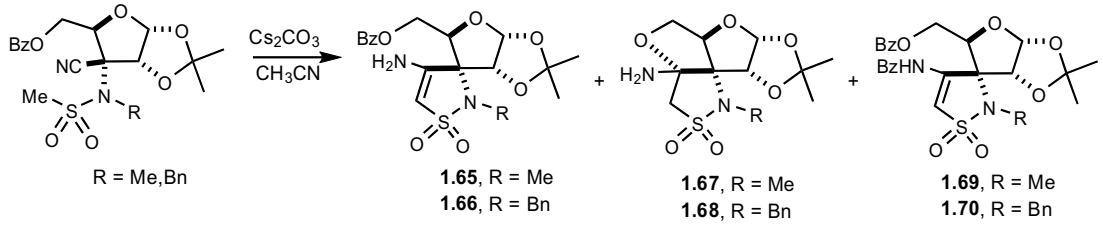
present in the sulfonamide substrate. For example, conversion of the *N*-methyl and *N*-benzyl sulfonamides ($R^2$) in Scheme 1.25 into the respective aminosultams was successfully achieved in good to excellent yields (59-99%) using $Cs_2CO_3$ (1 equiv.) as the base in refluxing MeCN for 1-2 h.

**Scheme 1.25**




However, when the analogous *N*-methyl- or *N*-benzyl-5-*O*-benzoyl derivatives (Scheme 1.26) were used as substrates, the expected cyclized products **1.65** and **1.66** were obtained. In addition, the basic conditions employed promoted hydrolysis of the benzoate to give the corresponding sultams **1.67** and **1.68** via Michael addition into the enamine followed by hydrolysis. Sultams **1.69** and **1.70** were obtained as a result of intramolecular benzoyl transfer (Scheme 1.26).

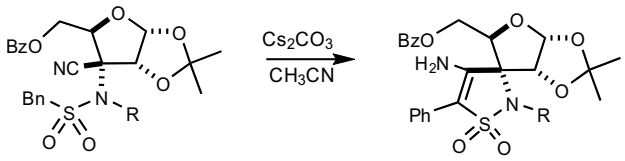
**Scheme 1.26**




When the α-benzyl substrates (Bn-$SO_2$NR) were used (Scheme 1.27), the desired cyclized products were obtained in excellent yields (R = Me, 98%; R = Bn, 99%) using the same reaction conditions as described above (Scheme 1.26). It seems

that the success of the reaction is also dependent upon the alkyl group located α to the sulfonamide functionality.

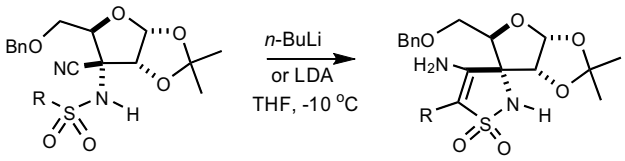
**Scheme 1.27**




R = Me, 98%
R = Bn, 99%

Interestingly, under similar reaction conditions ($Cs_2CO_3$ in $CH_3CN$) the unsubstituted (N-H) sulfonamides (Scheme 1.28) failed to provide the desired cyclized products. It is possible that deprotonation of the acidic proton from the nitrogen atom of the sulfonamide group forms the corresponding insoluble salt, thereby generating a heterogenous reaction mixture and impeding the cyclization step. However, by using a lithiated base such as *n*-BuLi or LDA (1 equiv.), the resulting lithium salt was expected to be soluble in THF allowing for cyclization. As predicted, treatment of the unsubstituted (N-H) sulfonamides with *n*-BuLi or LDA (1 equiv.) in THF afforded the respective sultams in marginal to excellent yields (Scheme 1.28).

**Scheme 1.28**



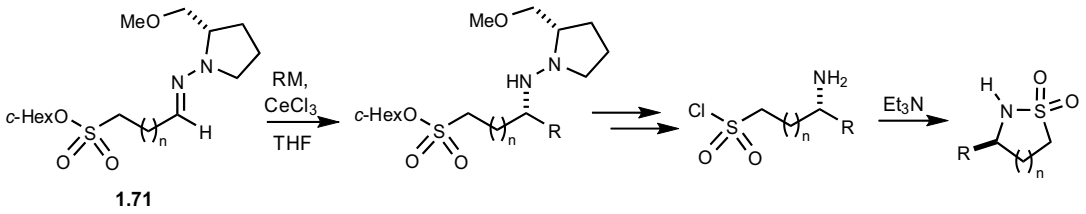

R = H, 99%
R = Me, 20%
R = Ph, 73%

In summary, *N*-substituted alkylsulfonamides cyclized successfully to the respective sultams in the presence of $Cs_2CO_3$, whereas for sulfonamides containing a

free N-H bond, *n*-BuLi or LDA proved to be the base of choice for the cyclization step.

In 2006, Enders and coworkers described a flexible synthesis of various γ- and δ-sultams.[79] A key step for the formation of the enantiopure sultams was the diastereoselective 1,2-nucleophilic addition to the C=N double bond of the hydrazonosulfonates. In this approach a chiral auxiliary (SAMP) was used to induced diastereoselectivity in the sulfonamide (Table 1.5). Chiral hydrazonosulfonate **1.71**

**Table 1.5** *Yields and enantioselectivities obtained for chiral sultams*




**1.71**

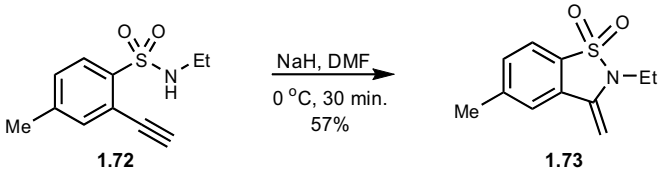
| R | n | Sultam (% yield) | % *ee*[a] |
|---|---|---|---|
| Et | 1 | 70 | 78 |
| *n*Bu | 1 | 99 | 87[b] |
| *n*Hex | 1 | 93 | 90[b] |
| Ph | 1 | 77 | 93 |
| Me | 2 | 82 | ≥ 96[b] |
| *n*Bu | 2 | 100 | 93 |
| *n*Hex | 2 | 100 | 93 |
| Ph | 2 | 72 | 99 |

a Determined by GC on chiral stationary phase (Chirasil-dex)
b In correlation with the *de* value of the corresponding hydrazines.

was subjected to 1,2-addition by organocerium reagents to install the alkyl group. Initial attempts to perform the nucleophilic addition with highly basic organolithium or Grignard reagents resulted in the elimination of the sulfur component. To avoid this problem, less basic but higher nucleophilic cerium reagents, formed by transmetallation of organolithium or Grignard reagents with dehydrated $CeCl_3$ were used. Under these conditions, various hydrazines were obtained in good to excellent yields (77-99%) and high diastereoselectivities (78 to $\geq$ 96%). Further transformations provided the sulfonyl chlorides which cyclized to the respective sultams under basic conditions ($Et_3N$). Five- and six-membered ring sultams were obtained in good to excellent yields (70-100%) and high enantiomeric excess (78-99%) with the six-memebered ring sultams providing the best *ee*'s (Table 1.5).

An interesting example of base promoted cyclization to sultams was reported by Snieckus and coworkers.[80] Attempted *N*-allylation of sulfonamide **1.72** under standard basic conditions (NaH, DMF, 0 °C), resulted in the exclusive formation of sultam **1.73** (Scheme 1.29) via an uncommon sulfonamide to acetylene 5-*exo*-*dig* ring closure.

**Scheme 1.29**

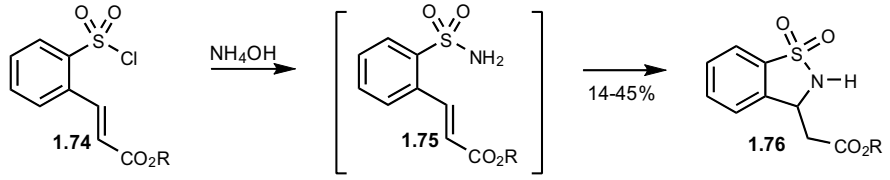



**1.72** **1.73**

A similar reaction occurred via an intramolecular Michael addition between the sulfonamide moiety and the α,β-unsaturated ester functionality in structure **1.75** (Scheme 1.30).[81] When attempting to transform sulfonyl chloride **1.74** into its

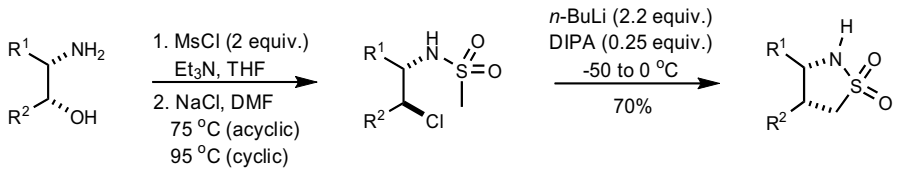
respective sulfonamide **1.75** by addition of a solution of ammonium hydroxide ($NH_4OH$), sultam **1.76** was obtained instead (Scheme 1.30). A variety of crystalline sultams resulted via this procedure albeit in low yields (14-45%).

**Scheme 1.30**



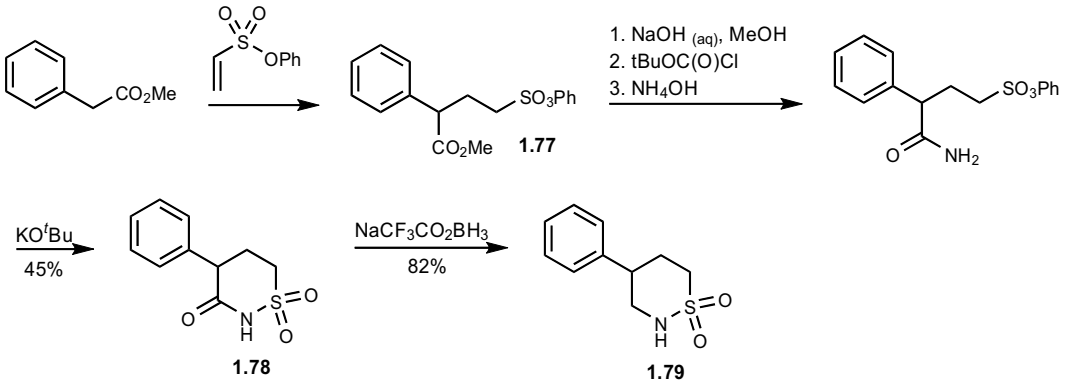

In 2003, Lee and coworkers reported a practical synthesis of sultams via sulfonamide dianion alkylation and the application of this method for the synthesis of chiral sultams as valuable chiral auxiliaries.[82] The chiral sultams were readily synthesized from commercially available β-amino alcohols. Their synthetic study revealed that methanesulfonylation of β-amino alcohols can be performed at both the hydroxyl and amino termini in the presence of $Et_3N$, followed by $S_N2$ displacement with sodium chloride (NaCl) in DMF to form sulfonamides in high yields (85-90%) (Scheme 1.31). Cyclization to sultams was readily initiated with the in situ generation of LDA[83] by treatment of *n*-BuLi (2.2 equiv.) and diisopropylamine (DIPA, 0.25 equiv.) at low temperatures (-50 °C). Subsequent aging of the reaction mixture at 0 °C for 1h provided a variety of chiral 5-membered ring sultams in good yields (68-75%) via this methodology. Based on the success of this synthetic approach, Merck applied it a year later to the multi-kilogram synthesis of a γ-secretase inhibitor as a potential target for the treatment of Alzheimer's disease.[84]

**Scheme 1.31**




Morris and coworkers set out to synthesize a variety of cyclic sulfonamides as potential sultam analogs of thromboxane $A_2$ ($TXA_2$) receptor antagonists.[85] Initial attempts began with a Michael reaction between a benzyl ester and vinyl sulfone to form the core substrate **1.77** (Scheme 1.32). Ester **1.77** was then converted to the amide via a three-step protocol, involving hydrolysis into the carboxylic acid followed by amination to afford the amide. The cyclization event to **1.78** was accomplished by the addition of KO$^t$Bu. Although the expected cyclization product was obtained, the yields were not quite satisfactory (45%). Finally, reduction of the carbonyl group with $NaCF_3CO_2BH_3$ provided sultam **1.79** in good yield (82%).

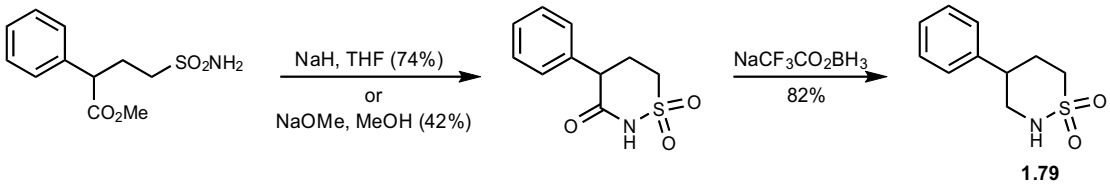
**Scheme 1.32**




Disappointed by the low yields provided via this route, an alternative synthesis was pursued in which the positions of the ester and sulfonamide moiety were switched. Cyclization of the sulfonamide (Scheme 1.33) provided the

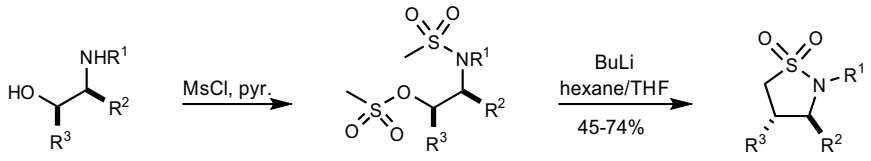
reaspective sulfimide in good yields in the presence of NaH (74%). Further conversion to sultam **1.79** via reduction of the carbonyl proceeded in good yield.

**Scheme 1.33**




In 1991, Cooper[86] reported a similar approach to Lee's[82] for the synthesis of sultams. The synthesis of aliphatic sultams was accomplished starting from 2-aminoalcohols. *N, O*-dimesylates, prepared by mesylation of the amino alcohols with MsCl and pyridine were treated with BuLi to give the respective sultams in moderate to good yields (45-81%) (Table 1.6).

**Table 1.6** *Results for the cyclization of N, O-dimesylates into sultams*



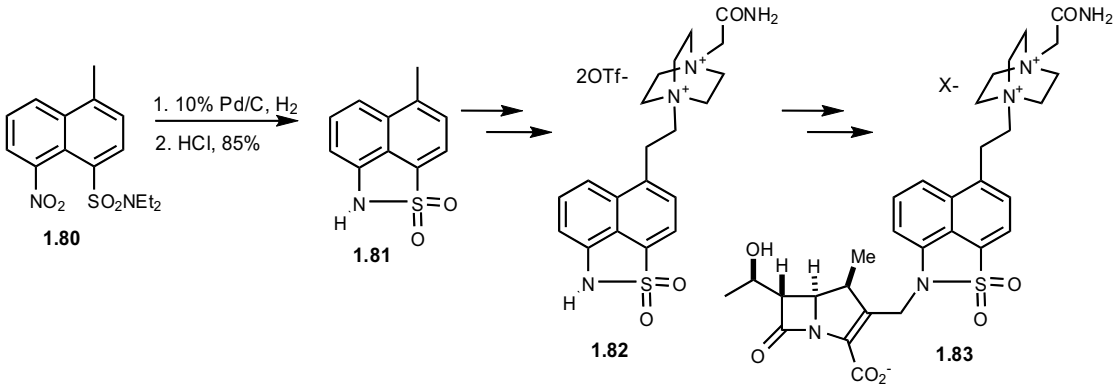

| $R^1$ | $R^2$ | $R^3$ | % yield of sultam |
|---|---|---|---|
| Bn | H | H | 74% |
| $-(CH_2)_3-$ | | H | 81% |
| Me | Me | Ph | 45% |

Although BuLi deprotonates both hydrogens α to the suylfonyl groups, only the anion generated from the *N*-mesylate can react efficiently in the intramolecular fashion to displace the *O*-mesylate, affording the cyclized products.

### 1.2.2.9 Acid-Promoted Cyclizations

In 2000, Merck Research Laboratories reported the acid-promoted cyclization to sultam **1.82**, which is a side chain of the β-lactam anti-MRSA (Methicillin-resistant *Staphylococcus aureus*) antibiotic **1.83**.[87] This side chain was identified as an anti-MRSA pharmacophore which was designed to be released upon opening of the β-lactam ring. The synthesis to this sultam was initiated from cheap, commercially available 1-methylnaphthalene. Sulfonylation and amination, followed by nitration of the aromatic ring afforded nitrosulfonamide **1.80** in modest yields. Cyclization to **1.81** was performed using a one-pot hydrogenation-cyclization reaction (Scheme 1.34).

**Scheme 1.34**

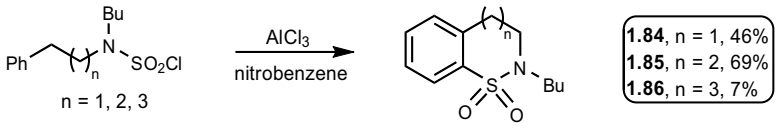



Reduction of the nitro group to the amine was accomplished by standard hydrogenation conditions (10% Pd/C, $H_2$) in quantitative yield. The aminosulfonamide intermediate was then cyclized upon acidification with HCl at

reflux for 3 h, providing sultam **1.81** in 85% yield and >99% purity after crystallization.

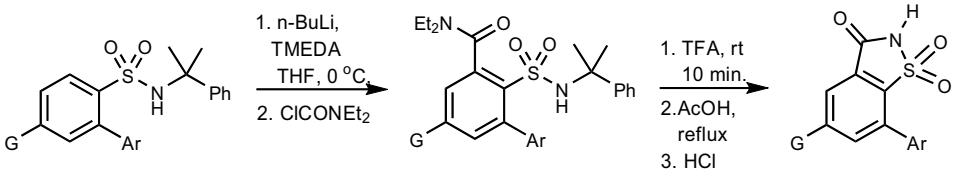
Lewis acids have also been utilized for the synthesis of sultams. Katritzky and coworkers reported the synthesis of 6-, 7-, and 8-membered ring aromatic sultams via a Friedel-Crafts cyclization of ω-phenylalkanesulfamoyl chlorides.[88] The Friedel-Crafts intramolecular cyclization reaction of the sulfamoyl chlorides shown in Scheme 1.35 was carried out in the presence of $AlCl_3$ in nitrobenzene. After aqueous workup, sultam **1.85** (n = 2, 69%) was obtained in high purity without the need for further purification, while sultams **1.84** (n = 1, 46%) and **1.86** (n = 3, 7%) required further chromatographic purification.

**Scheme 1.35**




In order to improve the yields of the sultam ring system present in saccharins, Snieckus and coworkers utilized an *ortho* metallation-cross coupling strategy, followed by cyclization under acidic conditions, to provide saccharin sultams in good to excellent yields[89] (Table 1.7). The metallation-cross coupling strategy of the sulfonamides proceeded via addition of *n*-BuLi/TMEDA, followed by *N*,*N*-diethylcarbamoyl chloride quench. Without isolation, addition of TFA, followed by treatment with HOAc provided the saccharin sultam systems shown in table 1.7 in modest to excellent yields (42-90%).

**Table 1.7** *Yields obtained for the formation of various saccharin sultams*

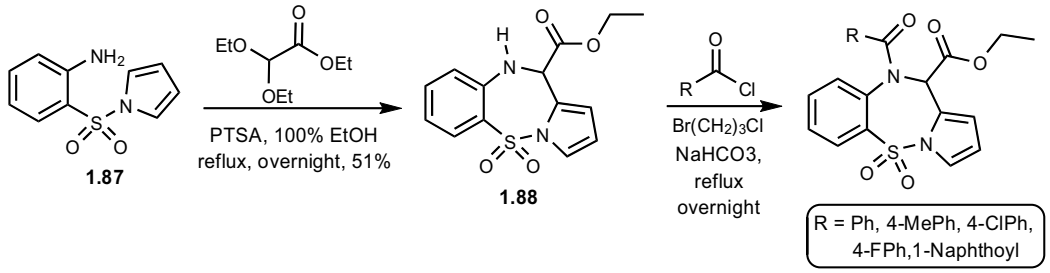



| % yield[a] of sultams | G | Ar |
|---|---|---|
| 90 | H | Ph |
| 57[b] | H | 2-naphthyl |
| 42[b] | Me | Ph |
| 88 | OMe | Ph |

a Isolated and purified products.
b Yield over two steps

In 2006, Silvestri and coworkers synthesized a series of 7-membered ring sultams via a Pictet-Spengler type cyclization.[37] Tricyclic sultam **1.88** was prepared in 51% yield via condensation between sulfonamide **1.87** and ethyl 2,2-diethoxyacetate in the presence of catalytic amounts of *p*-toluenesulfonic acid (PTSA) in refluxing absolute ethanol (100% EtOH) (Scheme 1.36). Acylation of sulfonamide **1.88** with various chlorides in the presence of $NaHCO_3$ and boiling 1-bromo-3-chloropropane afforded the respective amides. Biological testing performed on these compounds (also known as PBTDs) revealed that they are a new class of potential agents for the treatment of chronic myelogenous leukemia (CML). Derivatives of these promising compounds are currently being pursued in an effort to find new candidates for the treatment of cancer.

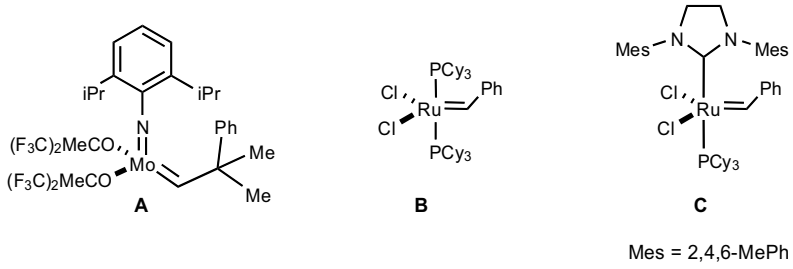
**Scheme 1.36**




### 1.2.2.10 Ring-Closing Metathesis (RCM)

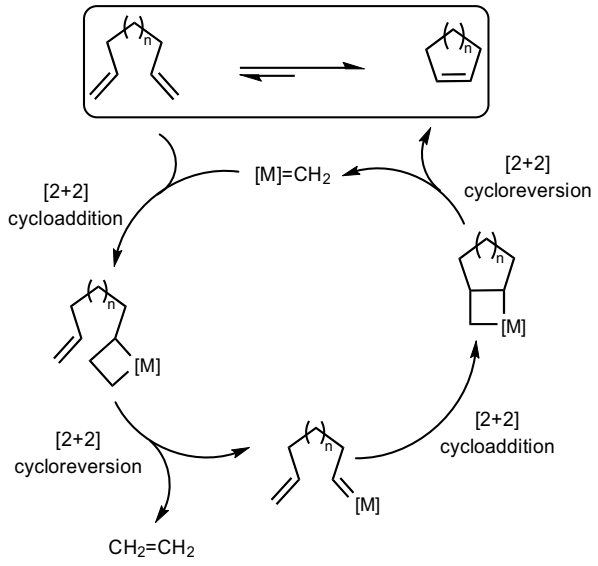
Ring-closing metathesis has emerged as a powerful synthetic tool for the formation of C-C bonds. A variety of well-defined alkylidine-metal complexes including the molybdenum complex **A**[90] and the ruthenium complexes **B**[91] and **C**[92] are available for this transformation (Figure 1.10). Even though molybdenum catalyst **A** exhibits very high reactivity towards a wide range of substrates, it suffers from extreme sensitivity to moisture and air as well as decomposition upon storage. While catalyst **B** is both air and water stable and compatible with many functional groups, it is not active for the formation of tri- and tetrasubstituted olefins.[92] The more active complex **C** has shown to be a powerful alternative, promoting the cyclization of tri- and tetrasubtituted olefins.[92]

**Figure 1.10** *Ruthenium and molybdenum catalysts used for RCM*



Initially, RCM was mostly used for the formation of carbocycles, but has found great applicability for the synthesis of heterocyclic rings, including sulfur heterocycles.[93] The RCM reaction has been used extensively for the formation of small to medium-sized rings as well as macrocycles. The mechanism by which this intramolecular C-C bond forming process takes place has been the topic of intensive study. The accepted RCM mechanism[94] is presented in Scheme 1.37. This pathway is initiated by the dissociation of a phosphine ligand to form a reactive 14-electron complex capable of coordinating an olefin. A [2+2] cycloaddition leads to the formation of a metallocyclobutane intermediate.[95] A [2+2] cycloreversion releases an ethylene molecule followed by a second [2+2] cycloaddition to form another, more sterically congested metallacyclobutane. A final [2+2] cycloreversion affords the cyclized product and regenerates the active catalytic species.

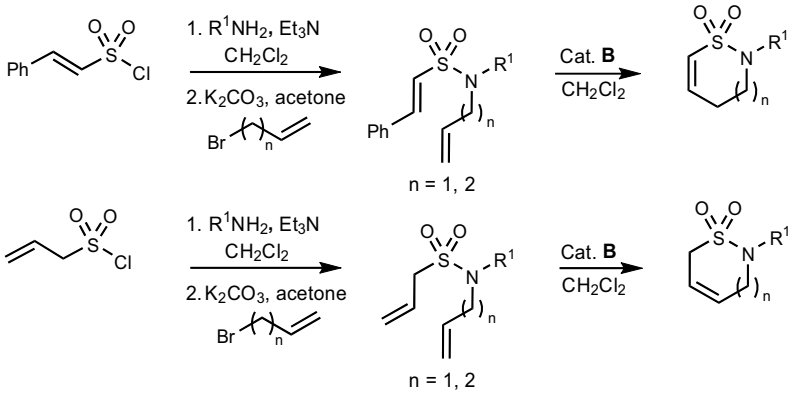
**Scheme 1.37**



Presented below is a summary of the RCM approaches that have been reported for the synthesis of sultams. Using this synthetic method, various ring-size sultams (5-, 6-, 7-, 8-, 9- and 15-membered ring) have been obtained. RCM routes to sulfamides and sulfamoyl carbamates will not be covered in this section as they are the basis of further discussions later in this dissertation.

The first report of the use of RCM for the efficient synthesis of sultams appeared in 1999 by Hanson and coworkers.[96] Novel 5-, 6-, and 7-membered ring allyl- and vinylsultams with different substituents at the nitrogen atom were accomplished using Grubbs first generation catalyst (Cat. **B**) (Figure 1.10). Styrenesulfonyl chloride and allylsulfonyl chloride proved to be ideal precursors to synthesize vinylsulfonamides and allylsulfonamides, respectively (Table 1.8). During the synthesis of allylsulfonamides, a minor product corresponding to vinylsulfonamide was observed. This product, arising from double bond isomerization of the allylsulfonamide during the base promoted allylation procedure was circumvented using benzylallylamine as the coupling partner with the allylsulfonyl chloride. The RCM products were obtained in good to excellent yields using 6 mol % of catalyst **B** (Figure 1.10) in refluxing $CH_2Cl_2$ at concentrations ranging from 0.01-0.02M. Interestingly, the cyclization of electron deficient olefins proved successful under the cyclization reaction conditions. It is worth mentioning that the cyclization of the sulfonamides bearing a free N-H was not deleterious to the performance of the catalyst, providing the respective cyclized products in excellent yields (90%).

**Table 1.8** *Results for the RCM cyclization of styrene and allylsulfonamides*

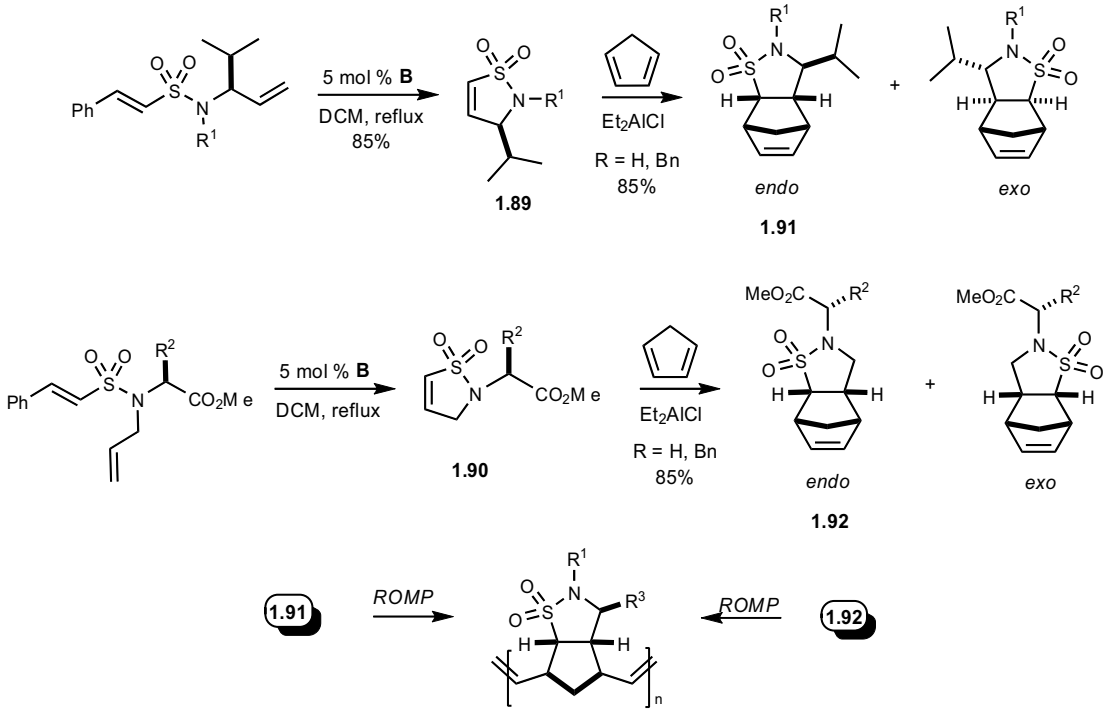



| $R^1$ | n | % Yield of RCM |
|---|---|---|
| H | 1 | 90 |
| Bn | 1 | 88 |
| Bn | 2 | 65 |
| $(CH)CH_2iPr(CO_2CH_3)$ | 1 | 90 |
| H | 1 | 90 |
| Bn | 1 | 91 |
| Bn | 2 | 91 |
| $(CH)CH_3(CO_2Et)$ | 1 | 87 |

In addition to these results, a strategy employing both RCM and Ring-Opening Metathesis Polymerization (ROMP) has been developed for the synthesis of oligimeric sultams.[97] The RCM precursors were synthesized following the same synthetic protocol as described in Table 1.8. Alkyl-substituted and amino ester-derived sulfonamides proved to be suitable substrates for the RCM reaction (Scheme 1.38). Cyclization to sultams **1.89** and **1.90** was carried out in excellent yields in the

presence of catalyst **B** (Figure 1.10), followed by subsequent Diels-Alder cyclization with cyclopentadiene under Lewis acid catalysis to form norbornenyl sultams as a mixture of separable diastereomers. The *endo* diastereomers **1.91** and **1.92** readily underwent ROMP with 1-20 mol % catalyst **B** (Figure 1.10) followed by quenching with ethyl vinyl ether to provide oligomeric sultams.

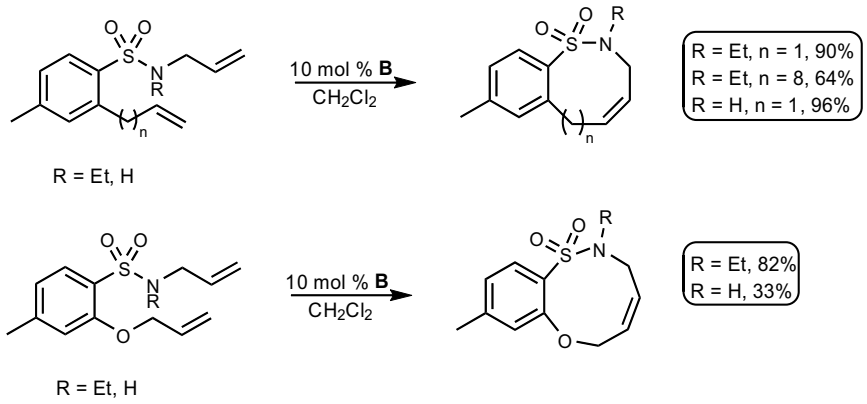
**Scheme 1.38**




Snieckus has described a directed *ortho* metalation-RCM approach for the synthesis of 7-, 8-, 9- and 15-membered ring sultams.[80] Aromatic *p*-toluene sulfonamides, bearing *N*-substituents (R = Et, allyl) underwent cyclization in good to excellent yields. The RCM reaction afforded 8- and 15-membered ring sultams (Scheme 1.39) using 10 mol % of catalyst **B** (Figure 1.10) in $CH_2Cl_2$ at rt for 16h. Dilute conditions (0.002M) were used for the cyclization step in order to avoid

dimerization as a result of cross-metathesis. The same ring-closing protocol proved useful for the synthesis of 9-membered oxygen-containing sultams (Scheme 1.39).

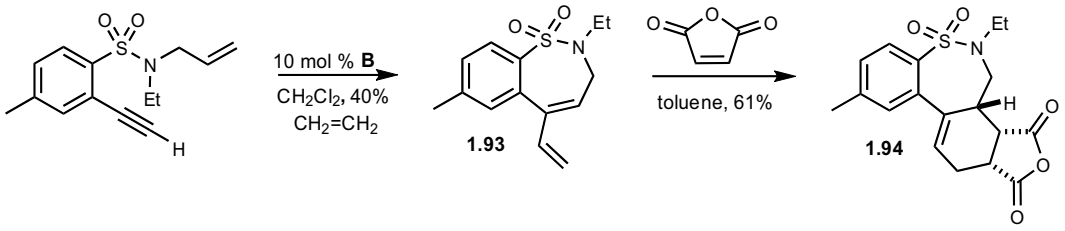
**Scheme 1.39**




The eight-membered ring sultams (n = 1, R = Et, H) were obtained in excellent yields (90-96%) while the 15-membered sultam (n = 8, R = Et) was obtained in good yield (64%) as a *cis:trans* mixture as determined by $^{1}$H NMR. In the nine-membered ring oxygen-containing sultams, the low yield obtained for the unsubstituted sultam (R = H, 33%) was attributed to isolation difficulty due to low solubility.

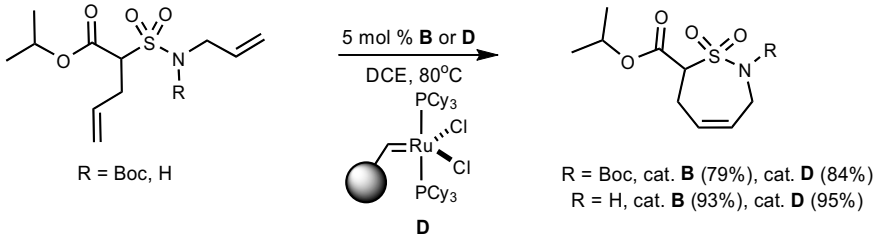
An enyne metathesis methodology was used for the synthesis of diene **1.93** (Scheme 1.40).[80] In this case the ene-yne precursor was exposed to similar RCM conditions as described above (Scheme 1.39) in the presence of an ethylene atmosphere in order to favor the formation of diene **1.93** (Scheme 1.40). This diene proved useful for further Diels-Alder cyclization with maleic anhydride, forming polycyclic sultam **1.94** in good yields.

**Scheme 1.40**




Two different RCM-cleavage strategies have also been implemented for the synthesis of sultams. In the first one, the RCM catalyst is bound to a polymer whereas the second strategy relies on polymer bound-substrates. In the first approach, a polymer bound RCM catalyst (Cat. **D**) (Scheme 1.41) developed by Barrett and coworkers[98, 99] has been utilized to synthesize 7-membered ring sultams with the ultimate goal of being incorporated into combinatorial chemistry and peptidomimetics.[100] The desire to use catalyst **D** for the generation of these entities arose from the difficulty of removing the ruthenium residues from the typical RCM reaction in conjunction to the difficulty of recycling the ruthenium catalyst from the reaction mixture. Exposure of the Boc-protected sulfonamide in Scheme 1.41 to 5 mol % catalyst **B** (Figure 1.10) or **D** in 1,2-dichloroethane (0.04M) provided the desired sultam in good yields (79% and 84% respectively). The RCM also proceeded efficiently at rt in 30 min. with the sulfonamide containing a free N-H bond using catalyst **B** or **D**, affording the respective 7-membered ring sultam in excellent yields (93% and 95% respectively). It is worth mentioning that the RCM reaction with catalyst **D** was accompanied by the addition of 1-hexene to the reaction mixture in order to facilitate the regeneration of the catalyst.

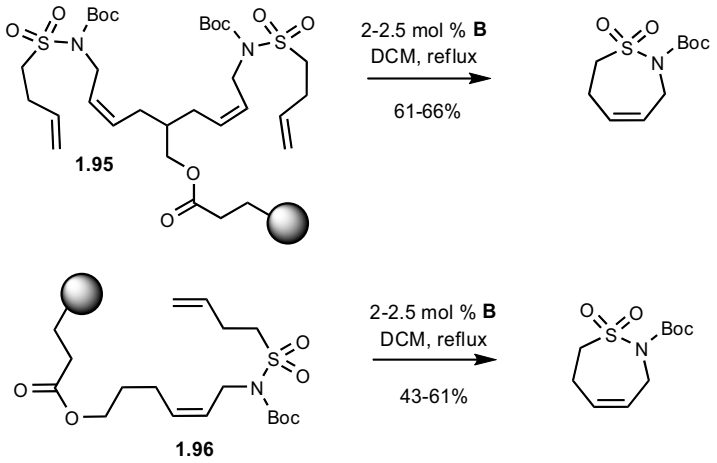
**Scheme 1.41**




The cyclized products using catalyst **D** were obtained pure without any residual ruthenium after a single chromatographic purification. Although catalyst **D** can be regenerated for further use via simple filtration, subjection to the RCM reaction conditions with recovered **D** resulted in a less active catalyst as evidenced by the lower yields obtained (46% yield for R = Boc and 54% yield for R = H).

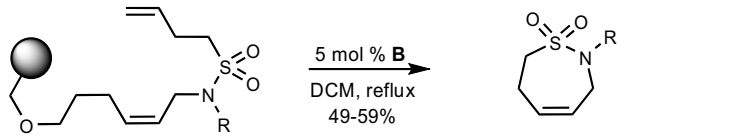
The second RCM-cleavage strategy has been applied to resin-bound sulfonamides, where the RCM reaction was effectively used to cleave the cyclized 7-membered ring sulfonamide from the resin.[101, 102] Double-armed and single-armed polystyrene precursors **1.95** and **1.96** were used to test the efficacy of this method. The RCM-cleavage strategy (Scheme 1.42) was performed with 2.5-5 mol % of cat. **B**

**Scheme 1.42**



(Figure 1.10) to afford the 7-membered ring sultam in good yields. The addition of an olefin co-factor (1-octene) to the reaction mixture resulted in a decrease in the yield of the cyclized product as well as a decrease in the crude purity. Investigations revealed that a double-armed linker was not necessary, therefore a variety of flexible single-armed linkers were used to obtained three different *N*-substituted sultams in moderate yields using only 5 mol % of catalyst **B** (Scheme 1.43).

**Scheme 1.43**

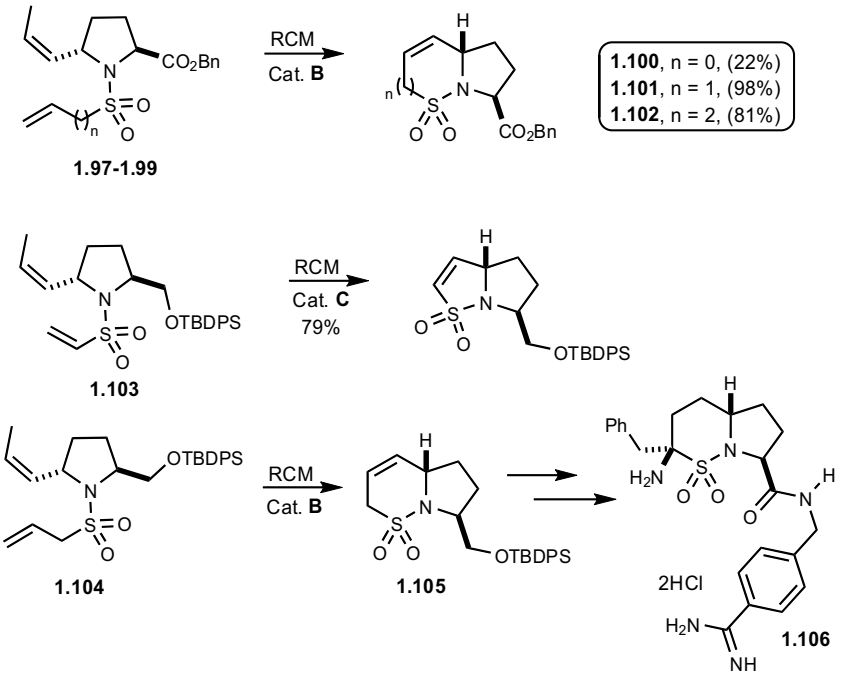



R = Boc (53%)
R = H (49%)
R = 2,5-dimethylbenzyl (59%)

The synthesis of a variety of bicyclic sultams as constrained proline analogs has been achieved by Hannesian and coworkers via RCM,[28] culminating in the synthesis of sultam **1.106** as a weak thrombin inhibitor (Scheme 1.44). Three types of bicyclic sultams varying in size of the sultam ring (5,5; 6,5; and 7,5) have been synthesized by this method (**1.100-1.102**) from sulfonamides **1.97-1.99** in good to excellent yields (Scheme 1.44). The RCM reaction was performed using 3-6 mol % of catalyst **B** (Figure 1.10) in refluxing $CH_2Cl_2$. While sulfonamide **1.100** (n = 0) was obtained in only 22% yield using catalyst **B**, the reaction with the more reactive catalyst **C** on the TBDPS protected ether **1.103** dramatically increased the yield of the product to 79%. Sultams **1.101** (n = 1) and **1.102** (n = 2) were obtained in excellent yields using catalyst **B**. Sulfonamide **1.104** containing an *O*-TBDPS protecting group

was cyclized to sultam **1.105** using 3 mol % of **B** and further used to obtain the thrombin inhibitor analog **1.106**.

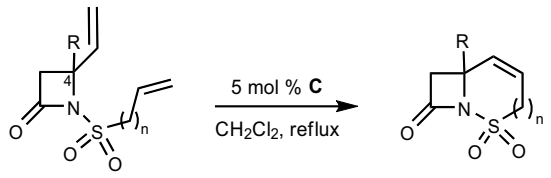
**Scheme 1.44**




A simple protocol for the rapid construction of sultams fused to a β-lactam ring as presented in Table 1.9 has been reported by Metz and coworkers as β-lactam sulfonamide hybrids.[103, 104] The β-lactams used were synthesized according to a published procedure and then converted to the *N*-sulfonyl derivatives. Initial attempts to cyclize vinylic sulfonamides (R = H, entry 1) and (R = Me, entry 2) with 5 mol % of catalyst **C** (Figure 1.10) in refluxing $CH_2Cl_2$ were unsuccessful. It is believed that enhanced ring strain of the bicyclic products might be an impeding factor. However, subjecting the allylic homologs (R = H, Me, entry 3 and 4) to the same RCM conditions afforded the desired bicyclic sultams in good to excellent yields (56% and 82%, respectively) as crystalline solids. The yields obtained for the

RCM reaction are presented below (Table 1.9). The best results were obtained for the seven-membered ring annelated sultams (n = 2, entry 5 and 6) regardless of the substituent present at the 4-position of the β-lactam ring. While six- and eight-membered ring sultams (R = Me, entry 4 and 8) were isolated in good yields (82% and 63%), cyclization to furnish the unsubstituted counterparts (R = H, entry 3 and 7) were less efficient, providing much lower yields (56% and 28%, respectively).

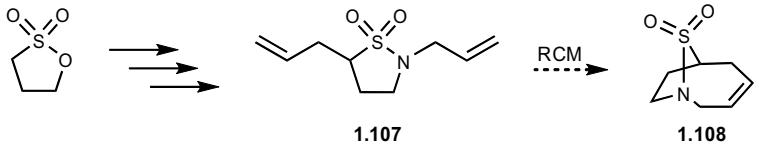
**Table 1.9** *Results for the RCM reaction towards fused sultams*




| Entry | R | n | % Yield of sultam |
|---|---|---|---|
| 1 | H | 0 | 0 |
| 2 | Me | 0 | 0 |
| 3 | H | 1 | 56 |
| 4 | Me | 1 | 82 |
| 5 | H | 2 | 98 |
| 6 | Me | 2 | 97 |
| 7 | H | 3 | 28 |
| 8 | Me | 3 | 63 |

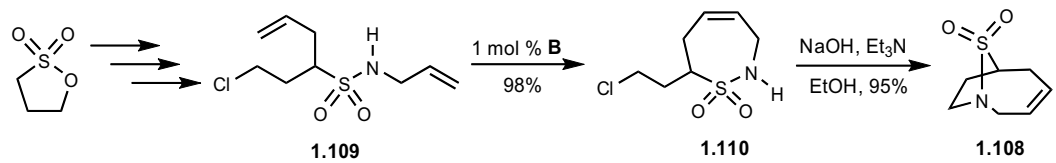
In 2006, Paquette and coworkers demonstrated the successful application of the RCM reaction for the synthesis of seven-membered ring sultams en routes to bicyclic sultams having a sulfur atom at the apex position.[105] This is the first report for the synthesis of bridgehead sultams of this nature. Initially, RCM to sulfonamide **1.107** was envisioned to be incorporated as the last step leading to the formation of bridgehead sultam **1.108**. This route began as a five-step sequence to afford the RCM precursor **1.107** (Scheme 1.45). Subjection of this diene to RCM conditions failed to provide bicyclic sultam **1.108**. The inability to perform the cyclization was attributed to a combination of ring strain and steric effects.

**Scheme 1.45**



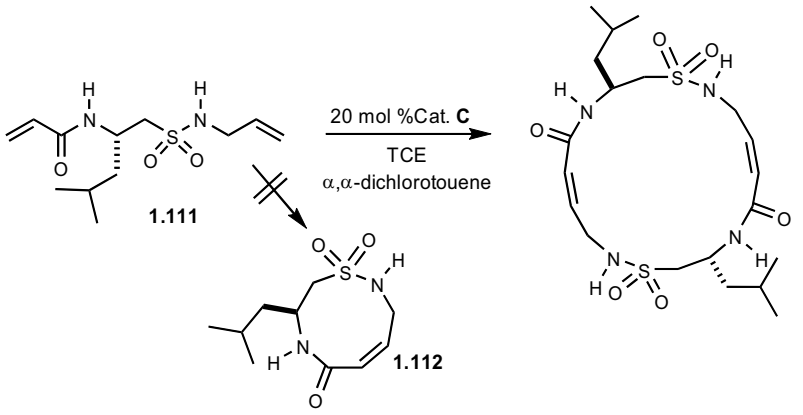

A solution to this problem was to rework the route to **1.108** by performing the RCM reaction at an earlier stage of the reaction sequence. With this in mind, sulfonamide **1.109** was subjected to the RCM reaction using only 1 mol % of catalyst **B** (Figure 1.10) to deliver sultam **1.110** in more than 90% yield (Scheme 1.46). Submission of the RCM product **1.110** to base-promoted cyclization readily formed bridgehead sultam **1.108** in high yield (95%).

**Scheme 1.46**



The synthesis of nine-membered ring peptidosulfonamides, although less prevalent in literature, has been achieved via RCM by Liskamp and coworkers.[106] Coupling of sulfonyl chloride with allyl amine in the presence of a weak base, followed by deprotection and subsequent reaction with acryloyl chloride provided the RCM precursor **1.111** (Scheme 1.47). The ring closure was performed using 20 mol % of catalyst **C** (Figure 1.10) in 1, 1, 2-trichloroethane as the solvent (10 mM). Interestingly, α,α-dichlorotoluene was added to the reaction mixture in order to reduce the inactivation of the catalyst. Unexpectedly, the dimeric 18-membered ring was the product obtained.

**Scheme 1.47**

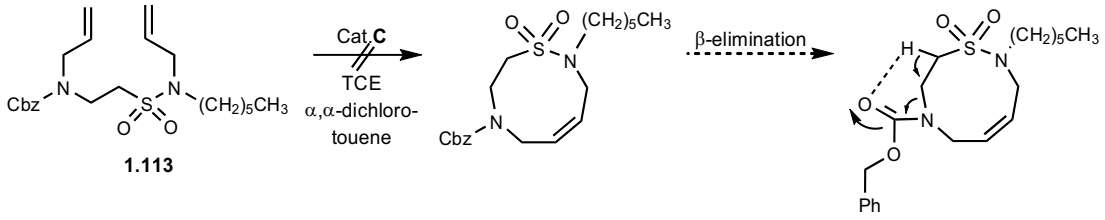



Further efforts to obtain the 9-membered ring sultam **1.112** by running the reaction under more diluted conditions (1 mM) were unsuccessful. It seems that the formation of the 18-membered ring is more favorable than the corresponding 9-membered ring for this particular substrate.

To facilitate the RCM reaction to a cyclic peptidosulfonamide structure, carbamate **1.113** was prepared. Subjection of **1.113** to the same RCM reaction

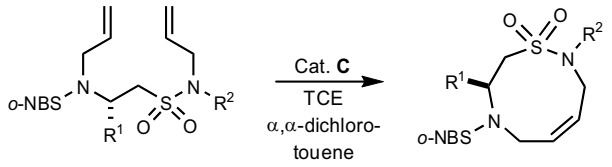
conditions as described in Scheme 1.47 failed to give the desired 9-membered sultam, forming instead a product arising presumably from ring opening by β-elimination (Scheme 1.48).

**Scheme 1.48**




Failed attempts to obtain the desired 9-membered ring sultams forced the authors to synthesize other RCM precursors keeping in mind that the sulfonamide moiety will facilitate a conformation in which the terminal alkenes will be favored to undergo ring closure. Switching the protecting group at the nitrogen from Cbz to *o*-NBS [the *o*-NBS-protecting (*o*-nitrobenzenesulfonyl) groups are less likely to accept a proton, therefore preventing β-elimination] was expected to facilitate the cyclization reaction. Using the same synthetic approach as explained before, three different sulfonamides (table 1.10, entry 1-3) were prepared in good yields and subjected to the RCM conditions using 10 mol % of catalyst **C** (Figure 1.10) to form the respective cyclic peptidosulfonamides in moderate to good yields (Table 1.10). These results indicate that peptidosulfonamides with different $R^1$ and $R^2$ groups are readily accessible via this method. These cyclic peptidosulfonamides were further incorporated into a peptide sequence to obtain β-turn mimetics.

**Table 1.10** *RCM approach towards sultam peptidomimetics*




| Entry | $R^1$ | $R^2$ | % yield of sultam |
|---|---|---|---|
| 1 | H | Bn | 60 |
| 2 | $CH_3$ | Cy | 47 |
| 3 | $CH(CH_3)_2$ | $(CH_2)_5CH_3$ | 48 |

## 1.3 Synthesis of Other Sulfur Heterocycles

The ability of the sulfonamide moiety to serve as a non-hydrolyzable amide surrogate, in conjunction to the successful application of the RCM reaction for the synthesis of sultams, has prompted efforts towards the synthesis of other sulfur analogs that can perhaps show biological activity. Sulfonamide analogs of interest include cyclic sulfamides, cyclic sulfamoyl carbamates and cyclic sulfamoyl ureas (see sections 1.3.2-1.3.5).

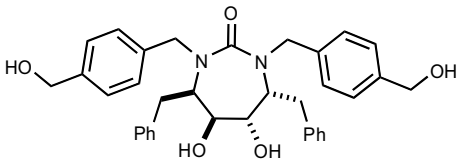
### 1.3.1 Cyclic Sulfamides

Sulfamides are compounds containing a sulfone functionality flanked by two nitrogen atoms ($R\text{-}NSO_2N\text{-}R^1$). Although a variety of biologically active cyclic sulfamides have been reported, the sulfamide analogs of the HIV protease inhibitor DMP 323 (Figure 1.11) have been of much interest in our group.

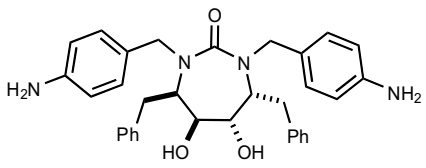
### 1.3.2 DMP 323 and Related Analogs

In 1994, scientists at DuPont Merck Laboratories reported the development of a variety of highly potent HIV protease inhibitors.[107] Based on X-ray crystallographic data which shows that HIV PR exists as a $C_2$-symmetric dimer, DuPont Merck initially pursued the synthesis of nonpeptidic $C_2$-symmetric inhibitors with the hope of combining adequate potency with oral bioavailability. A variety of promising inhibitors were synthesized and screened, out of which the seven-membered ring urea DMP 323 exhibited good activity against HIV PR ($IC_{90}$ = 57 mM) (Figure 1.11).[107] Despite its good oral bioavailability in animals, phase I clinical trial studies were disappointing, resulting in the withdrawal of the molecule as a consequence of high blood level variability in humans.[108] The more water soluble candidate DMP 450[109] (Figure 1.11) was then synthesized showing an improved pharmacokinetic profile in humans during its phase I clinical trials. However, its promising therapeutic value was hindered by high plasma protein binding.[109] As a result, the search for new candidates with improved pharmacokinetics became an ongoing effort.

**Figure 1.11** *Cyclic ureas DMP 323 and DMP 450*



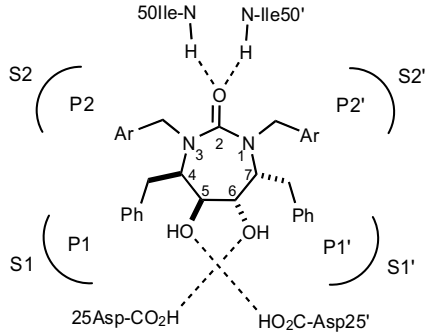

*DMP 323*
$IC_{90}$ = 57 nM
$K_i$ = 0.34 nM




*DMP 450*
$IC_{90}$ = 130 nM
$K_i$ = 0.28 nM

Extensive SAR studies have been concentrated on determining the effect of varying the P1/P1'/P2/P2' residues in DMP 323 (Figure 1.12). This has allowed for a better understanding of its interaction with the enzyme, facilitating the development of new analogs with improved pharmacokinetic properties. It was found that varying the P1/P1'/P2/P2' residues in DMP 323 significantly influence inhibitory potency by accentuating hydrophobic (P1/P1'), hydrogen bonding (P2/P2') and catalytic aspartate (diol functionality) interaction with the enzyme. It has also been of major interest to determine the absolute stereochemistry of its four contiguous stereocenters (4*R*, 5*S*, 6*S*, 7*R*)[110] in order to make possible the synthesis of related analogs with improved potency.

**Figure 1.12** *General features of the cyclic ureas developed by DuPont Merck*

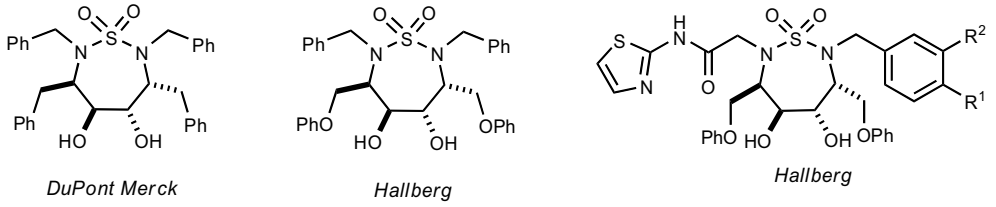



### 1.3.3 Sulfamide Analogs of DMP 323

While the cyclic ureas have been of much interest, studies conducted independently by DuPont Merck Laboratories scientists,[111] Hallberg and coworkers [112-115] and Karlén and coworkers[116] revealed that sulfamide analogs of DMP 323 also display inhibitory activity (Figure 1.13). In addition, unsymmetric urea[117-120] and sulfamide[116] derivatives of DMP 323 were also studied due to their potential to

exhibit different solubility and inhibitory profiles relative to their $C_2$-symmetric counterparts.

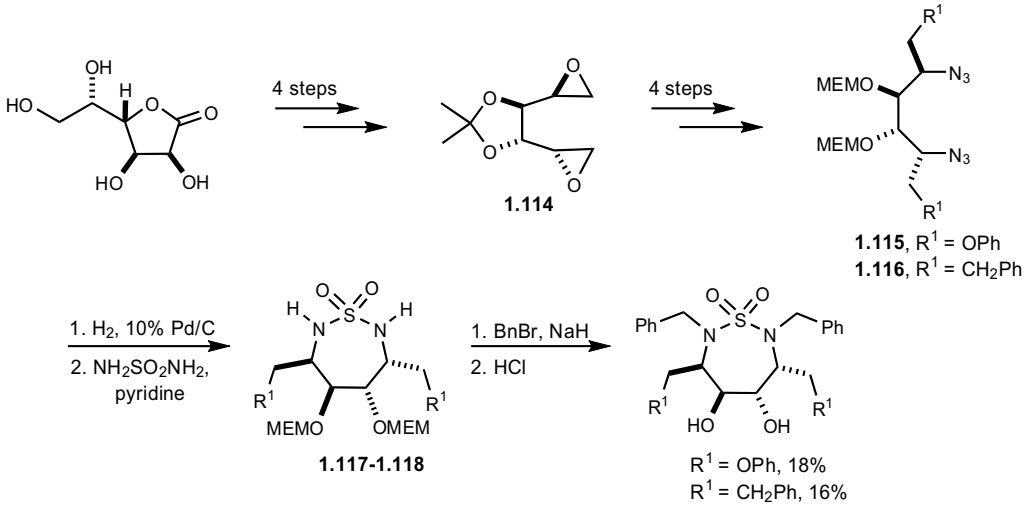
**Figure 1.13** *Symmetric and unsymmetric sulfamide analogs of DMP 323*




### 1.3.4 Synthetic Approaches Towards Sulfamide Analogs of DMP 323

The synthesis of $C_2$-symmetric sulfamide analogs of DMP 323 commenced with bisepoxide **1.114** as the key intermediate. For the preparation of bisepoxide **1.114** a four-step protocol was followed starting from commercially available L-mannonic γ-lactone (Scheme 1.49). [108, 112] Bisepoxide **1.114** was subjected to ring opening, Mitsunobu alkylation, and various protection-deprotection protocols to afford diazides **1.115** and **1.116**. Reduction of these diazides under standard hydrogenation conditions ($H_2$, 10 % Pd/C) afforded the respective diamines. The crude reaction mixture of the diamines was treated with sulfamide in pyridine to form sulfamides **1.117** and **1.118**. Benzylation with NaH, followed by *O*-MEM group removal with dry HCl in ether-methanol provided the sulfamide analogs of DMP 323 ($R^1$ = OPh) and ($R^2$ = $CH_2Ph$) in 18% and 16% overall yield, respectively from bisepoxide **1.114**. This reported route required 12 overall steps to get to the desired $C_2$-symmetric sulfamides in low overall yields. It is worth mentioning that this synthetic route incorporates the sulfamide moiety at the late stages of the synthesis.

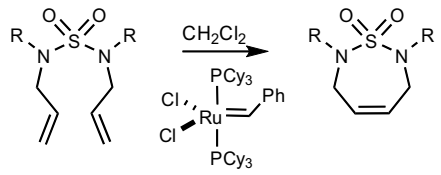
**Scheme 1.49**




The synthesis of unsymmetric sulfamide analogs of DMP 323 have also been reported.[116] These analogs have been achieved by simple *N*-alkylation of sulfamides **1.117** and **1.118** (Scheme 1.49) under basic conditions. However, this protocol provided a mixture of products including the desired unsymmetric analogs as well as the symmetric analogs and recovered **1.117** and **1.118**.

Based on our previous success on the ring-closing metathesis strategies to cyclic sulfamide peptidomimetics (Scheme 1.50),[121] we envisioned to implement the RCM reaction to obtain both symmetric and unsymmetric sulfamide analogs of DMP 323. A detailed explanation towards this endeavor will be discussed in Chapter 3.

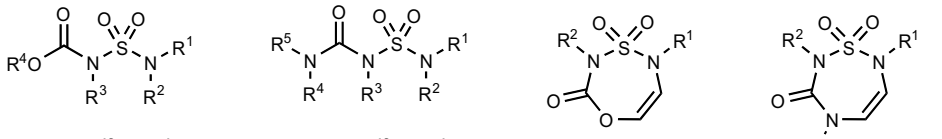
**Scheme 1.50**



### 1.3.5 Cyclic Sulfamoyl Carbamates and Sulfamoyl Ureas

Cyclic sulfamoyl carbamates and sulfamoyl ureas are among another class of *S*-heterocycles of much interest in our group. Sulfamoyl carbamates (Figure 1.14) have been primarily used as important synthetic intermediates in the synthesis of unsymmetric sulfamides[93, 121, 122] and sulfahydantoins.[123] These compounds have been studied as acetyl-CoA:cholesterol O-acyl-transferase (ACAT) inhibitors[124] in conjunction with sulfamoyl ureas (Figure 1.14). While examples of acyclic sulfamoyl carbamates are prevalent in the literature, reports of their cyclic counterparts are still limited, with only two examples, **1.119** and **1.120** reported to date (Figure 1.15).[125]

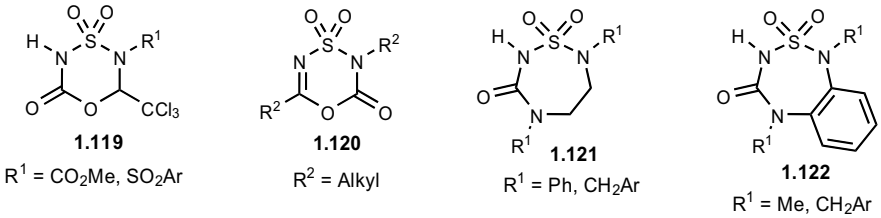
**Figure 1.14** *Representative structures of sulfamoyl carbamates and sulfamoyl ureas*




Sulfamoyl ureas (Figure 1.14) have been shown to be important hypoglycemic agents,[126-129] ACAT inhibitors,[124] and herbicides.[130, 131] Although large libraries of sulfamoyl ureas have been synthesized, cyclic sulfamoyl ureas have been largely unexplored, with only one report in literature containing structures **1.121** and **1.122** (Figure 1.15).[132]

A detailed explanation of the RCM approach utilized to access a variety of cyclic sulfamoyl carbamates and sulfamoyl ureas will be covered in Chapter 4.

**Figure 1.15** *Examples of cyclic sulfamoyl carbamates and sulfamoyl ureas*




## Conclusions

Based on the important properties encountered in sulfonamides, sultams, and related sulfur analogs, the synthesis of more novel variants should be explored in hopes of generating promising candidates for the treatment of life threatening illnesses affecting humanity such as cancer and AIDS. With a variety of synthetic methods described so far for the facile construction of sultams, the RCM reaction seems very promising for the facile access to a variety of *S*-heterocycles. With the effectiveness of the RCM reaction for the quick construction of *S*-heterocycles, the generation of important pharmacologically active targets containing this functionality is within reach.

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## Chapter 2

*A Facile RCM Strategy to Functionalized Sultams: Development of Scaffolds with Multiple Handles for Diversification and Library Development*

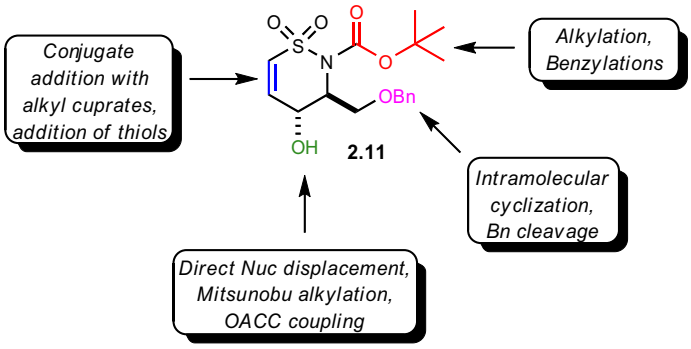
The aforementioned broad spectrum of biological activity displayed by sulfonamides, sultams and related sulfur heterocycles described in the introductory chapter (Chapter 1) has prompted us to develop new methods for their synthesis. This in turn has opened opportunities for the development of diversification strategies for the production of their corresponding libraries. Sulfonamides, sulfamides, sulfamoyl carbamates and sulfamoyl ureas outlined in chapter 1 represent ideal functional moieties that can serve as nonhydrolyzable amide surrogates. When coupled with additional desirable chemical features, they represent promising peptidomimetic scaffolds for library production. Our interest in the construction of novel *S*-heterocycles has recently led us to assemble a series of related sultams using a strategy based on RCM, which is the basis of this chapter. The facile assembly via RCM and versatility of a key γ-hydroxy vinyl sultam (**2.11**) are the cornerstone of this approach.

## 2.1 Synthetic Strategies Towards Sultam Scaffolds

Our proposed strategy towards the synthesis of a diverse array of sultam scaffolds hinges on several key points, including: (1) multi-gram scale synthesis of allyl sulfonyl chloride which will be used as a sulfur linchpin for the installation of the sulfonamide moiety, (2) installation of additional complexity via Mitsunobu reaction with enantiomerically pure building blocks, (3) cyclization utilizing the RCM reaction and subsequent manipulation en route to a key γ-hydroxy vinyl sultam, and (4) incorporation of both solution phase strategies and ROMP-derived reagents for the diversification of each scaffold (Scheme 2.1). The simplicity of this approach

has enabled the production of sultam scaffolds in multi-gram scale using 6-7 step solution phase protocols. The development of "scaffolds from scaffolds", where a common core structure can give access to a variety of diversified products is also of primary aim. An example of one of the sultam scaffolds of interest containing multiple handles for diversification and library development is shown in Figure 2.1. Polymer-assisted solution phase chemistry will be made possible through the employment of high-load, immobilized ROMP reagents that have been produced on large scale in our laboratories. Overall, our ultimate aim is to utilize this strategy towards the generation of novel sultams with biological and synthetic utility.

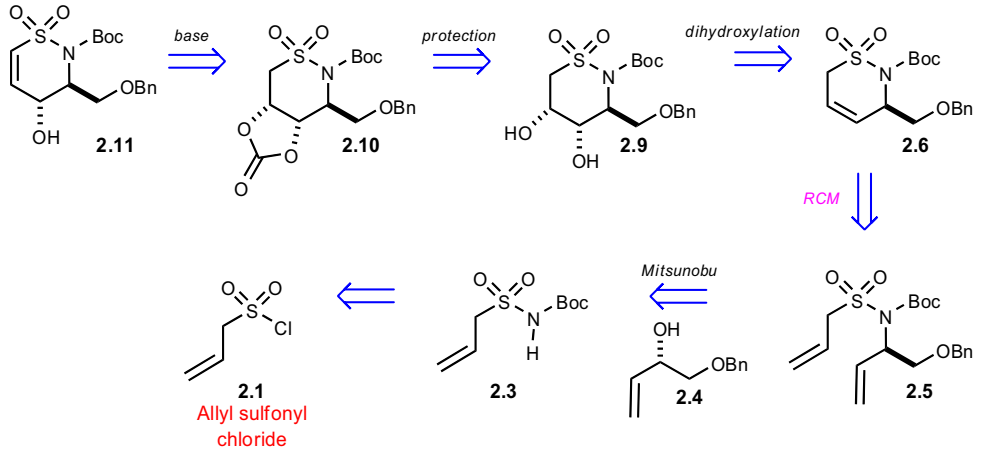
**Figure 2.1** *Scaffold of interest and possible diversification reactions*




Our synthetic strategy to access sultam scaffold **2.11** (Figure 2.1) is outlined in Scheme 2.1. A retrosynthetic analysis towards this endeavor suggested the use of the readily prepared allyl sulfonyl chloride (**2.1**)[1] as the starting material of choice (Scheme 2.1). Conversion of sulfonyl chloride **2.1** into sulfamoyl carbamate **2.3** will set the stage for the installation of chiral building blocks via Mitsunobu alkylation. Use of RCM will allow for the generation of sultam scaffolds of general structure **2.6**. Diastereoselective osmium-mediated dihydroxylation, subsequent carbonate

formation and base-promoted elimination of the cyclic carbonate **2.10** will yield the desired C(4)-γ-hydroxy vinyl sultam **2.11**. This scaffold was envisioned to be transformed into a variety of other complex structures using established protocols in our previous work related to *P*-sugars,[2] as well as new protocols developed within this dissertation.

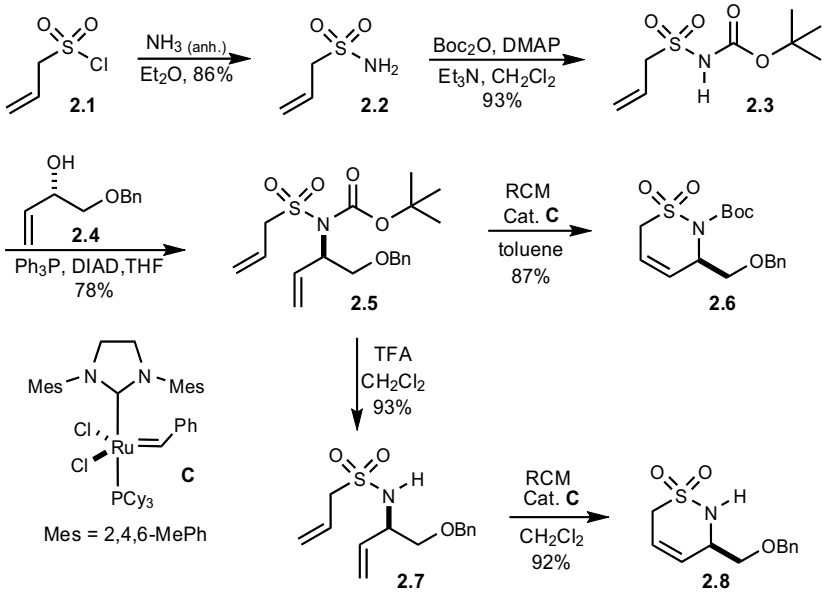
**Scheme 2.1**




Our strategy towards sultam **2.6** began with the multi-gram production of allyl sulfonyl chloride (**2.1**) following the two-step protocol developed by Belous and coworkers[1] (Scheme 2.2). Thus, conversion of allyl sulfonyl chloride (**2.1**) into sulfamoyl carbamate **2.3** was achieved via a two-step sequence that involved amination of **2.1** using anhydrous ammonia in ether to form sulfonamide **2.2**,[1] followed by Boc-protection of sulfonamide **2.2** via slow addition of di-*tert*-butyl dicarbonate ($Boc_2O$) in the presence of $Et_3N$ in $CH_2Cl_2$ at rt.[3] This process provided sulfamoyl carbamate **2.3** in excellent yield (96%) along with a minor byproduct (less than 4% yield) arising from bis-protection. Both compounds were easily separable by column chromatography. The introduction of the Boc group in

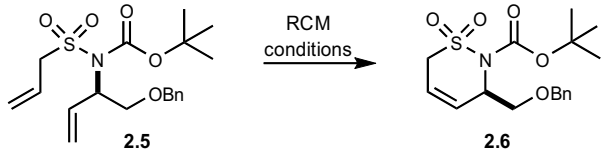
sulfamoyl carbamate **2.3** served a dual purpose: (1) as a labile protecting group that can be easily removed at any stage for further diversifications, and (2) as a group that proved to be essential in lowering the pKa of the N-H (pKa ~ 4) in sulfamoyl carbamate **2.3** for further Mitsunobu alkylation. Mitsunobu reaction of sulfamoyl carbamate **2.3** was performed with the readily prepared, chiral, nonracemic alcohol **2.4**, obtained from the condensation of trimethyl sulfonium ylide ($Me_2S{=}CH_2$) with (*S*)-benzyl glycidyl ether,[4] in the presence of DIAD and $PPh_3$ in THF at rt to generate diene **2.5** in good yield (78%). During the optimization of the Mitsunobu reaction it was observed that the yield of diene **2.5** was dependent upon the concentration of the reaction. When the reaction was performed under dilute conditions (0.05M), diene **2.5** was obtained in the highest yield (78%) due to the formation of the product primarily originated from the desired $S_N2$ pathway rather than the competing $S_N2'$ route. However, performing the reaction at higher concentrations (0.1M or higher), resulted in a significant decrease in yields (40-51%) and an increase in the formation of a byproduct arising from a $S_N2'$ pathway as clearly evidenced by TLC and confirmed by NMR analysis. With diene **2.5** in hand, we concentrated our efforts on the cyclization step to generate sultam **2.6**. Initial attempts to perform the RCM reaction with diene **2.5** using $CH_2Cl_2$ or $ClCH_2CH_2Cl$ (DCE) as solvents under refluxing conditions resulted in unsuccessful RCM. However, cyclization of diene **2.5** using toluene as the solvent under refluxing conditions afforded the desired product **2.6**.

**Scheme 2.2**




Various RCM conditions were studied and the results shown in Table 2.1. The optimized conditions for the RCM reaction were realized in the presence of 5 mol % of Grubbs second generation catalyst (cat-**C**)[5] in refluxing toluene under dilute conditions (0.01-0.005M), to provide sultam **2.6** in 87% yield (entry 3, Table 2.1). Performing the RCM reaction with the Grubbs first generation catalyst (catalyst **B**)[6] resulted in comparable yields, although higher catalyst loadings as well as longer reaction times were required (entry 4, Table 2.1). Removal of residual ruthenium was achieved using DMSO according to the method of Georg.[7]

**Table 2.1** *Results obtained for the RCM reaction with diene **2.5***



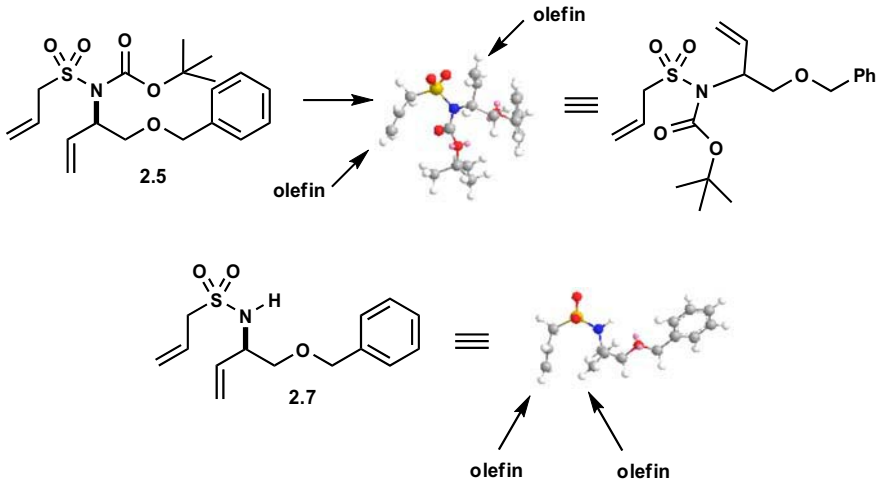

**2.5** **2.6**

| Entry | RCM Conditions | % yield RCM Product |
|---|---|---|
| 1 | 5 mol % Cat. **C**<br>$CH_2Cl_2$, 45 °C | NR |
| 2 | 5 mol % Cat. **C**<br>$ClCH_2CH_2Cl$, 83 °C | NR |
| 3 | 5 mol % Cat. **C**<br>toluene, 110 °C | 87% |
| 4 | 10 mol % Cat. **B**<br>toluene, 110 °C | 84% |

Molecular modeling[8] was performed in order to provide insight into the outcome of the RCM reaction. It was observed that the presence of vicinal disubstitution at N-2 ($SO_2N$-Boc) and C-3 ($CH_2OBn$) in diene **2.5** forces the terminal olefins to be oriented in opposite directions (Figure 2.2). This unfavorable conformation necessitated the use of a higher boiling point solvent, refluxing toluene, for successful RCM. In contrast, the RCM reaction for diene **2.7** possessing a free sulfonamide N-H ($SO_2N$-H) should proceed at lower temperatures since molecular modeling revealed that the olefins in diene **2.7** are in close proximity to each other. In order to test this hypothesis, the Boc group was removed from sulfamoyl

carbamate **2.5** (Scheme 2.2) under acidic conditions using TFA[9] in $CH_2Cl_2$ at rt to afford diene **2.7** in excellent yield (93%), which was then readily cyclized to sultam **2.8** in high yield (92%) using 5 mol % of catalyst **C**[5] in refluxing $CH_2Cl_2$. It is worth mentioning that the presence of a free N-H bond in sulfonamides **2.7** did not negatively affect the performance of the catalyst during the RCM reaction as is sometimes the case with allylic amides possessing free N-H bonds.[10]

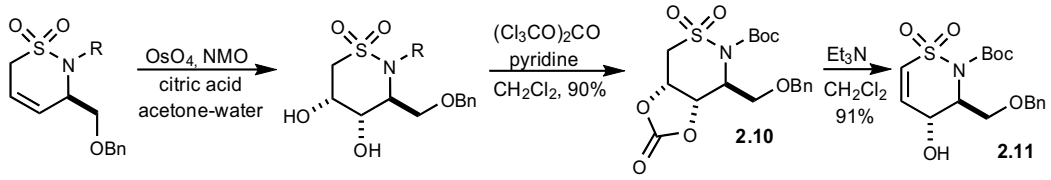
**Figure 2.2** *Molecular modeling performed for dienes **2.5** and **2.7***




Efforts towards the desired C(4)-γ-hydroxy vinyl sultam **2.11** continued with dihydroxylation of sultam **2.6** (Scheme 2.3). Thus, osmium-catalyzed dihydroxylation[11] of sultam **2.6** in the presence of NMO and citric acid in a mixture of acetone and water as solvents resulted in the formation of the *cis*-diol **2.9** in high yield (96%) and excellent diastereoselectivity (*dr* > 99:1). The absolute configuration of diol **2.9** was unambiguously confirmed by X-ray crystallography (see Appendix). Sultam **2.8** containing a free N-H was also subjected to identical dihydroxylation conditions to afford diol **2.12** in high yield (94%) as a mixture of inseparable

diastereomers (*dr* ~ 8:1). With the high diastereoselectivities obtained for diol **2.9**, we continued our synthetic route to sultam **2.11**. Thus, diol **2.9** was protected as the carbonate **2.10** in excellent yield (90%) using triphosgene and pyridine in $CH_2Cl_2$.[12] Base-promoted elimination of carbonate **2.10** with $Et_3N$ in refluxing $CH_2Cl_2$ afforded C(4)-γ-hydroxy vinyl sulfonamide **2.11** in high yield (91%).

**Scheme 2.3**

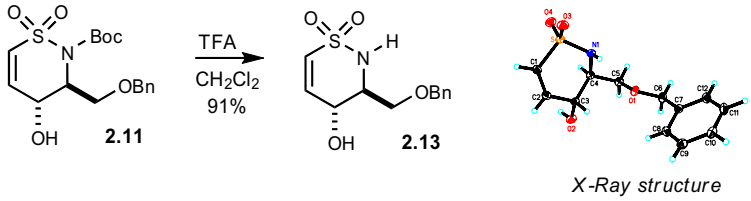



**2.6**, R = Boc
**2.8**, R = H

**2.9**, R = Boc, 96% (*dr* > 99:1)
**2.12**, R = H, 94% (*dr* ~ 8:1)

Removal of the Boc-group using the aforementioned acidic conditions (TFA, $CH_2Cl_2$)[6] afforded **2.13** as a crystalline solid in high yield (91%). Single crystal X-ray analysis of sultam **2.13** confirmed the absolute configuration (Scheme 2.4)

**Scheme 2.4**




*X-Ray structure*

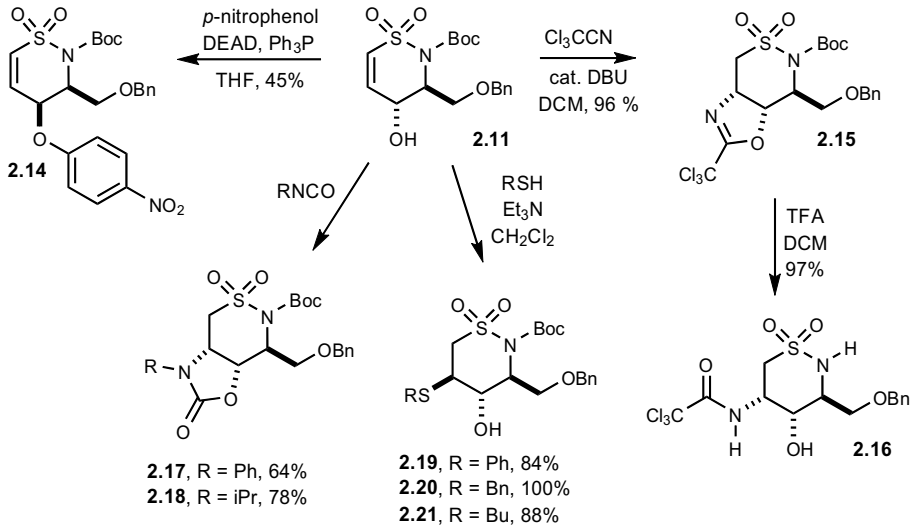
## 2.2 C(4)-γ-hydroxy Vinyl Sultam: A Versatile Scaffold

With C(4)-γ-hydroxy vinyl sultam **2.11** in hand we proceeded to perform a variety of diversification strategies using solution phase protocols as outlined in Scheme 2.5. Thus, initial *O*-functionalization via Mitsunobu reactions of vinyl sultam **2.11** using different substituted phenols as nucleophiles was attempted. It is

worth mentioning that the Mitsunobu reaction of **2.11** proceeded only with phenols bearing electron withdrawing groups. Mitsunobu alkylation of sultam **2.11** using DEAD and $PPh_3$ in THF at rt was successful when using *p*-nitrophenol as the nucleophile (Scheme 2.5) to afford *O*-diversified sultam **2.14** in moderate yield (45%). However, Mitsunobu reaction with phenol or *meta*-*tert*-butylphenol failed to provide the respective *O*-diversified sultam, while Mitsunobu reaction with *para*-bromophenol afforded only traces of the desired product.

We then turned our attention to the introduction of nitrogen at the C(3) position in efforts to obtain amino alcohols. Consequently, vinyl sultam **2.11** was treated with trichloroacetonitrile ($Cl_3CCN$) in the presence of catalytic amounts of DBU in $CH_2Cl_2$ to afford trichloroacetimidate[2] **2.15** in excellent yield (96%). Further treatment of **2.15** with TFA in $CH_2Cl_2$ at rt afforded amino alcohol **2.16** in 97% yield (Scheme 2.5).

**Scheme 2.5**

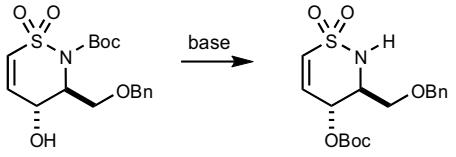


We also explored the addition of isocyanates to vinyl sultam **2.11** in attepts to form bicyclic sultams. Treatment of **2.11** with phenyl isocyanate (PhNCO) and $Et_3N$ in $CH_2Cl_2$ at reflux afforded sultam **2.17** in good yield (64%) via conjugate addition into the vinylic double bond (Scheme 2.5). Interestingly, when isopropyl isocyanate (iPrNCO) was utilized under identical conditions, prolonged reaction times were necessary in order to obtain the cyclized product **2.18** in good yield (78%).

We then turned our attention towards the possibility of performing conjugate addition of nucleophiles at the C(3) position of vinyl sultam **2.11**. Previous work reported by Roush and coworkers[13] has revealed that vinyl sulfonamides are excellent Michael acceptors of sulfur nucleophiles. Based on the success of this report, we attempted the addition of various thiols at C(3) of vinyl sultam **2.11** (Scheme 2.5). Addition of thiophenol (PhSH) to sultam **2.11** in the presence of catalytic amounts of $Et_3N$ in $CH_2Cl_2$ at rt[14] afforded sultam **2.19** in good yield (84%) as a mixture of inseparable diastereomers (dr ~ 6:1) as determined by $^1H$ NMR. With the success of this reaction, different thiols were explored. Interestingly, addition of phenylmethane thiol ($PhCH_2SH$) under the identical reaction conditions afforded sultam **2.20** in quantitative yield (100%) as a separable mixture of diastereomers with improved diastereoselectivity (dr ~ 10:1). Addition of butane thiol resulted in the formation of sultam **2.21** in 88% yield as a mixture of inseparable diastereomers (dr ~ 4.5:1). 2-methylpropane-2-thiol [$(CH_3)_3CSH$], however, failed to undergo Michael reaction under the same reaction conditions, presumably due to steric factors.

An interesting result was obtained during the course of this study. When γ-hydroxy sultam **2.11** was subjected to basic reaction conditions using 1.1 equiv. of $Cs_2CO_3$ in THF at 60 °C for 1 h, an unexpected product originating from Boc-group migration onto the alkoxide providing sultam **2.22**, was isolated in 71% yield (Table 2.2). Schreiber and coworkers have previously reported a similar Boc-group migration event.[15] In order to determine the extent of the Boc-group migration, a variety of bases were studied. Interestingly, it was observed that Boc-group migration also occurred in the presence of $K_2CO_3$ (entry 2, 76%) and NaH (entry 3, 91%). However, subjecting sultam **2.11** to 1.1 equiv. of $Et_3N$ in $CH_2Cl_2$ at reflux for 1 h resulted in complete recovery of **2.11**. These results open the door for further diversification reactions with sultam **2.22**. Diversification efforts utilizing sultam **2.22** will be pursued in the near future.

**Table 2.2** *Results for Boc migration observed in sultam **2.11***

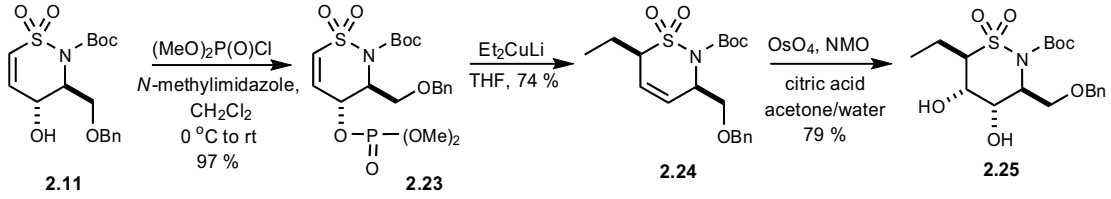



**2.11** **2.22**

| Entry | Base | % yield of **2.22** |
|---|---|---|
| 1 | $Cs_2CO_3$ | 71% |
| 2 | $K_2CO_3$ | 76% |
| 3 | NaH | 91% |
| 4 | $Et_3N$ | 0% |

We have also been interested in the installation of alkyl groups at the α-position of sultam **2.11** with the final goal of incorporating different functional groups throughout the periphery of the ring. In order to accomplish this, we reasoned that the introduction of an excellent leaving group such as a phosphate[16] at the oxygen atom of the hydroxyl group will favor this process. With the leaving group in place, it was expected that conjugate addition with organocuprates will introduce the desired alkyl group at the α-position of **2.11**. Thus, coupling of $(MeO)_2P(O)Cl$ with sultam **2.11** in the presence of *N*-methylimidazole in $CH_2Cl_2$ at 0° C afforded allylic phosphate **2.23** in excellent yield[17] (97%) (Scheme 2.6). Conjugate addition of ethyl cuprate to **2.23**[18] was performed by adding an excess (10 equiv.) of diethylzinc cuprate to phosphate **2.23**, affording sultam **2.24** in good yield (74%). This product was further dihydroxylated under osmium-catalyzed conditions[11] to afford *cis*-diol **2.25** in good yield (79%).

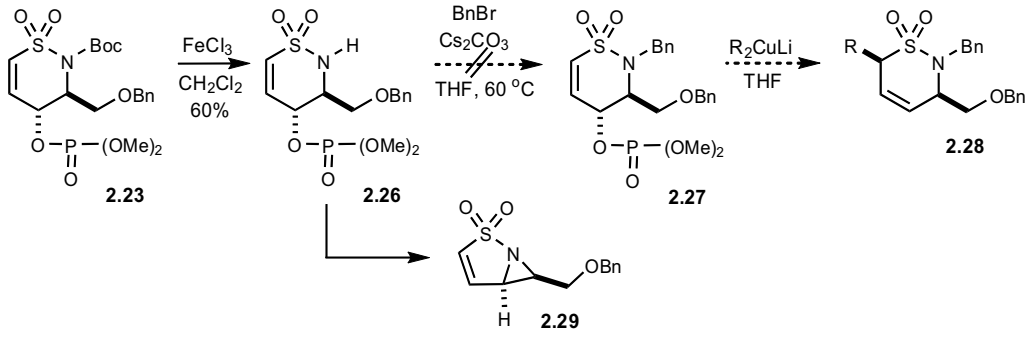
**Scheme 2.6**




With the success of the reaction sequence presented in Scheme 2.6, we turned our efforts to performing a diversification/cuprate addition strategy. This approach involving deprotection via removal of the *N*-Boc group, followed by benzylation at the new free N-H site, followed by organocuprate addition will generate sultam **2.28** (Scheme 2.7). Initial attempts to remove the Boc group in sultam **2.23** using TFA in

$CH_2Cl_2$ resulted also in the hydrolysis of the phosphate moiety. We therefore turned our attention to exploring milder reaction conditions that will remove the Boc group while leaving the phosphate moiety untouched. To our delight, treatment of sultam **2.23** with 1-1.5 equiv. of $FeCl_3$[19] in $CH_2Cl_2$ at rt for 30 min. afforded, after aqueous workup, sultam **2.26** in good yield (60%). Attempted *N*-benzylation of sultam **2.26** under basic conditions (BnBr, $Cs_2CO_3$, THF, 65 °C) did not afford the desired *N*-benzyl sultam **2.27**. Instead, a product lacking both the phosphate moiety as well as the *N*-benzyl group was isolated and later confirmed to be aziridine **2.29** via NMR analysis. This product was presumably the result of direct nucleophilic displacement at C(4) bearing an excellent leaving group. Failed attempts to obtain sultam **2.28** via this route led us to abandon this reaction sequence. In addition, studies concerning this remarkable internal $S_N2$ displacement are underway.

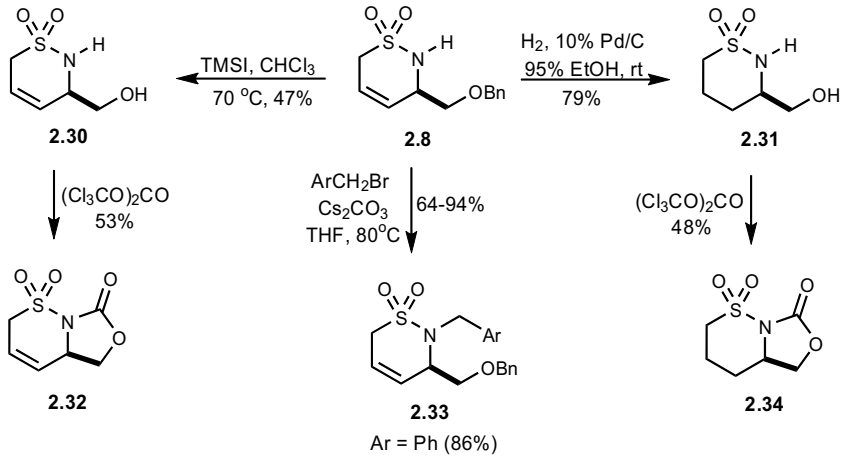
**Scheme 2.7**




With the successful generation of scaffold **2.11** and its multiple diversification reactions performed, efforts were directed at the diversification of scaffold **2.8** as outlined in Scheme 2.8. Thus, alkylation of nitrogen using benzyl bromide and $Cs_2CO_3$ in THF at 80 °C for 30 min. afforded sultam **2.33** in good yield (86%). This

reaction was successfully performed with a variety of benzyl bromides to afford the respective benzylated sultams in good to excellent yields (64-94%). Formation of conformationally constrained sultams was also of much interest. Simultaneous removal of the benzyl group and double bond in sultam **2.8** was accomplished via hydrogenation[20] to afford sultam **2.31** in good yield (79%). Formation of carbamate **2.34** was accomplished in moderate yield (48%) using triphosgene in pyridine.[12] Alternatively, the olefin may be conserved through removal of the benzyl group with TMSI[21] to afford sultam **2.30** in moderate yield (47%). Subsequent formation of carbamate **2.32** proceeded in good yield (53%). Overall, sultam **2.8** represents a simple scaffold from which to generate diversified compounds with chemical and potential biological utility.

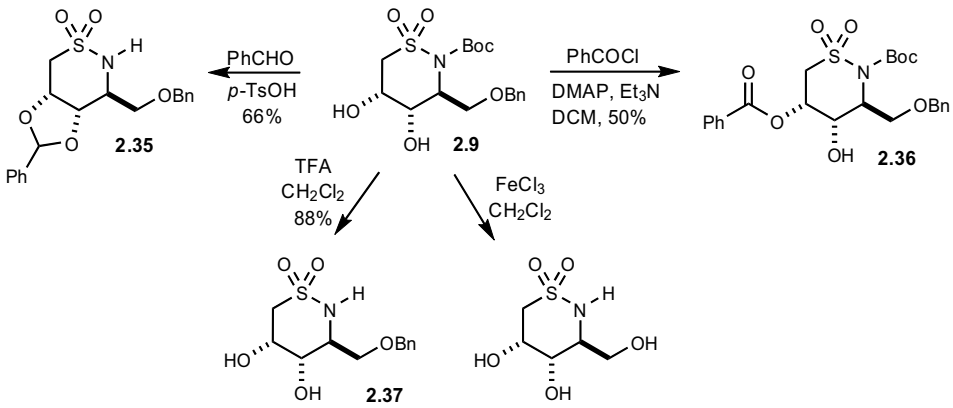
**Scheme 2.8**




Our next diversification strategy was concentrated on sultam **2.9** as outlined in Scheme 2.9. Reaction of diol **2.9** with benzaldehyde and *p*-TsOH in refluxing benzene[22] provided acetal **2.35** as a mixture of separable diastereomers (dr ~1:1) in a combined yield of 66%. Monoacylation of diol **2.9** was then performed. Thus,

reaction of diol **2.9** with benzoyl chloride[23] and $Et_3N$ in $CH_2Cl_2$ at 0 °C afforded sultam **2.36** in moderate yield (50%). We then turned our attention to the synthesis of unexplored sugar-like sultams. Thus, treatment of diol **2.9** with TFA in $CH_2Cl_2$ afforded sultam sugar **2.37** in 88% yield, while treatment with 5 equiv. of $FeCl_3$ in $CH_2Cl_2$ at rt for 1 h afforded the respective sultam triol as a single baseline spot by TLC. Aqueous workup was necessary to quench $FeCl_3$, however, the polarity of the resulting triol has thus far hampered isolation. Efforts focusing on non-aqueous workup are underway.

**Scheme 2.9**



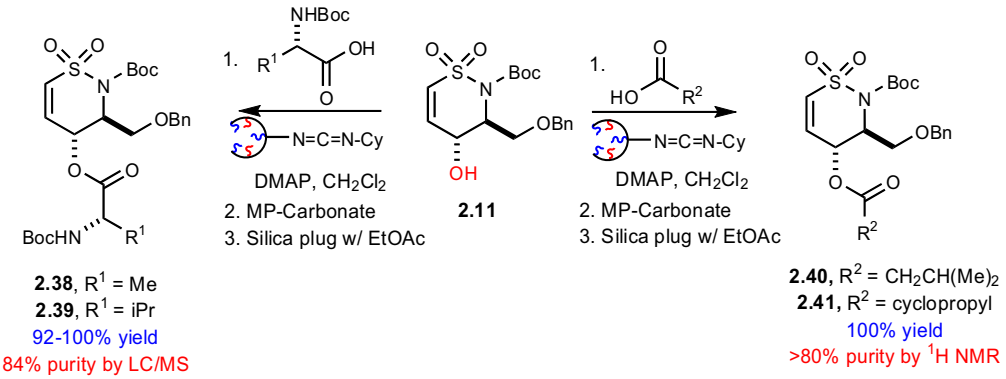

So far, a concise RCM pathway for the generation of multi-gram quantities of different scaffolds has been developed. We have devised a "scaffold from scaffold" strategy that has relied on the use of solution phase protocols for different diversification strategies. With the success of these diversification reactions we next explored the use of polymer supported reagents or ROMP reagents for implementation in diversification strategies and generation of sultam libraries.

## 2.3 Use of ROMP Reagents for Diversification Strategies and Development of Sultam Libraries

With the success obtained so far with diversification reactions performed using solution phase protocols we concentrated our efforts on the application of ROMP reagents previously developed in our laboratories to facilitate the generation of combinatorial libraries. The use of polymer-supported reagents will allow for the generation of diversified products by using filtration as the sole method of purification, avoiding the need for column chromatography which is a typical bottleneck in conventional solution phase techniques. We have previously reported the successful coupling of a variety of primary amines and alcohols with carboxylic acids using the coupling reagent OACC,[24] which is our polymer version of DCC. We have been able to successfully synthesize OACC in our laboratories in multi-gram quantities and use it effectively in a variety of coupling reactions with cyclic sulfamide scaffolds.[25] We therefore explored the application of OACC to the coupling reaction of sultam **2.11** with different amino acids. The coupling reaction of C(4) γ-hydroxy sultam **2.11** with Boc-protected (L)-valine and Boc-protected (L)-alanine was performed using OACC in the presence of catalytic amounts of DMAP in $CH_2Cl_2$ at rt for 12 h. The commercially available basic resin MP-carbonate was utilized to scavenge the excess amino acid used in the coupling reaction. Simple filtration via a plug of silica using 100% EtOAc as eluent successfully afforded sultam **2.38** and **2.39** in excellent yields (92% and 100%, respectively) and high purities (>84%) as determined by LC/MS (Scheme 2.10).

The same OACC coupling protocol was successfully performed using sultam **2.11** and carboxylic acids such as isovaleric acid and cyclopropane carboxylic acid to afford sultams **2.40** and **2.41** in excellent yields (100%) and high purities (>80% by $^1$H NMR).

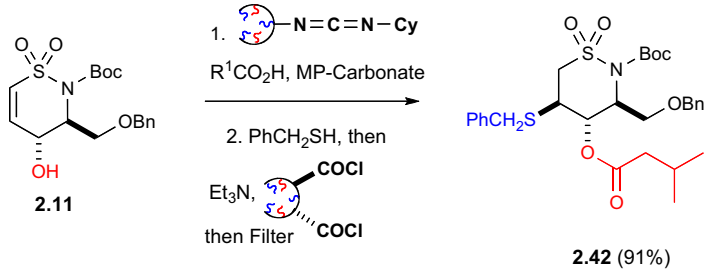
**Scheme 2.10**




The successful application of OACC for the coupling reactions presented above, in conjunction to the successful addition of thiols to sultam **2.11** presented in Scheme 2.5, prompted our efforts towards the development of a one-pot protocol involving OACC coupling of sultam **2.11** with carboxylic acids followed by addition of thiols. This strategy will provide a protocol for the bis-functionalization in a one-pot procedure. Thus, sultam **2.11** was subjected to OACC coupling with isovaleric acid under the same reaction conditions as explained before to generate sultam **2.40** (Scheme 2.11). After the scavenging event with MP-carbonate and filtration through a silica plug with 100% EtOAc, sultam **2.40** was immediately treated with phenylmethane thiol in $CH_2Cl_2$ at reflux for 12 h, followed by scavenging of the thiol nucleophile with OBAC,[26] a ROMP-generated bis-acid chloride designed in our

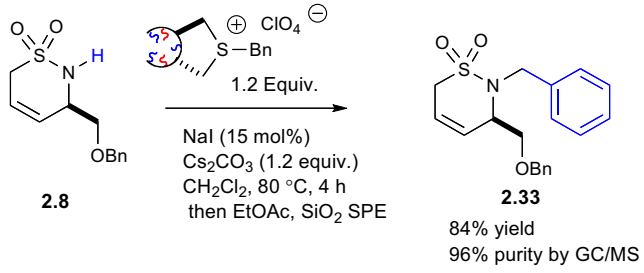
laboratories for the scavenging of nucleophiles. This procedure provided diversified sultam **2.42** in good yield (91%) and >80% purity based on $^1$H NMR as a mixture of inseparable diastereomers (dr ~ 6:1) after simple filtration through a plug of silica.

**Scheme 2.11**




We have also been able to develop a variety of new ROMP-derived benzylating agents and showed its successful application towards the benzylation of amines, phenols, benzenethiols, sulfonamides and sultams.[27] Thus, sultam **2.8** was benzylated by addition of 1.2 equiv. of the ROMP-derived benzylsulfonium salt in the presence of $Cs_2CO_3$ (1.2 equiv.) and NaI (15 mol %) at 80 °C in $CH_2Cl_2$ for 4 h, followed by simple filtration through a silica plug using 100% EtOAc as eluent (Scheme 2.12). The benzylated sultam **2.32** was obtained in good yield (84%) and high purity (96%) as determined by GC/MS. This protocol exemplifies the facile

**Scheme 2.12**

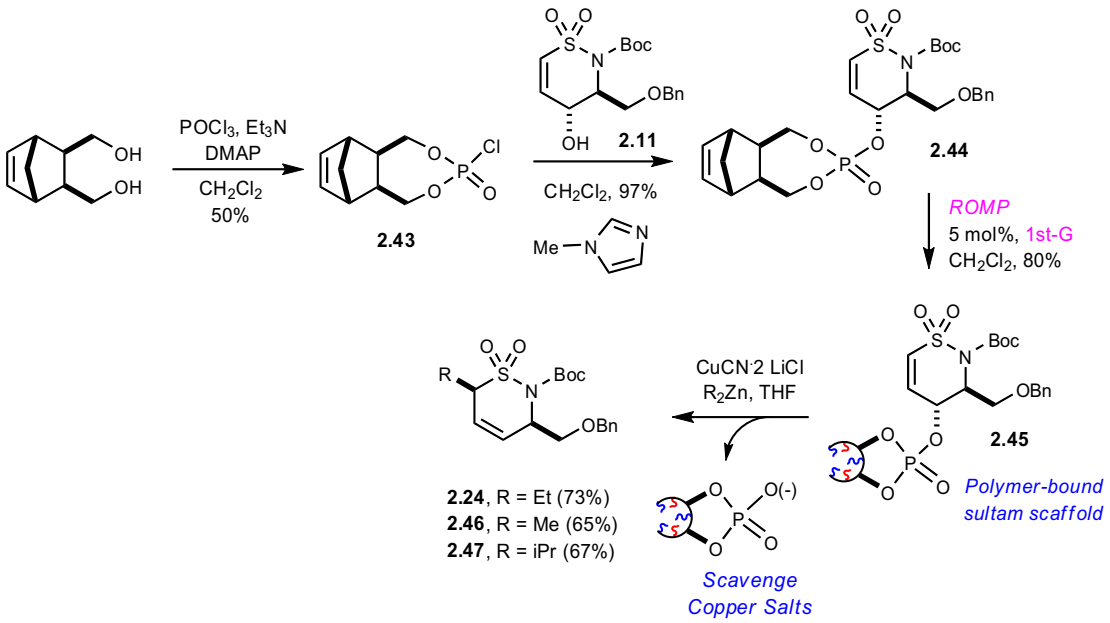


access to diversified sultams by utilizing ROMP-derived reagents where filtration is used as the sole method of purification.

Our efforts were then concentrated on the possibility of polymerizing the sultam scaffold **2.11**, followed by a diversification reaction involving addition of organocuprates and simple filtration to readily obtain α-alkylated sultams. Thus, commercially available 5-norbornene-2-*exo*,3-*exo*-dimethanol was transformed into the respective norbornenyl monochlorophosphate tag **2.43** via coupling with freshly distilled $POCl_3$ in the presence of $Et_3N$ and DMAP in $CH_2Cl_2$ in good yield (50%) (Scheme 2.13). The coupling reaction of norbornenyl monochlorophosphate tag **2.43** with sultam **2.11** under basic conditions utilizing *N*-methylimidazole in $CH_2Cl_2$, afforded sultam **2.44** in an excellent 97% yield. Polymerization of the tagged sultam scaffold **2.44** was possible using 5 mol % of Grubbs first generation catalyst (cat-**B**) in $CH_2Cl_2$ at reflux to obtain the polymer-bound sultam **2.45** in good yield (80%). This polymer-bound sultam was subjected to the aforementioned conjugate addition with various alkyl organocuprates to afford α-alkylated sultams **2.24** (R = Et, 74%), **2.46** (R = Me, 65%) and **2.47** (R = iPr, 67%) in good yields and high purity (>90%) after simple filtration via silica plug with 100% EtOAc.

It was observed that the ROMP-derived phosphate played a dual role during the organocuprate-release event: (1) it served as an excellent leaving group for the conjugate addition of the organocuprate and (2) upon release, it served as a scavenger to sequester the copper salts formed during the reaction conditions.

**Scheme 2.13**

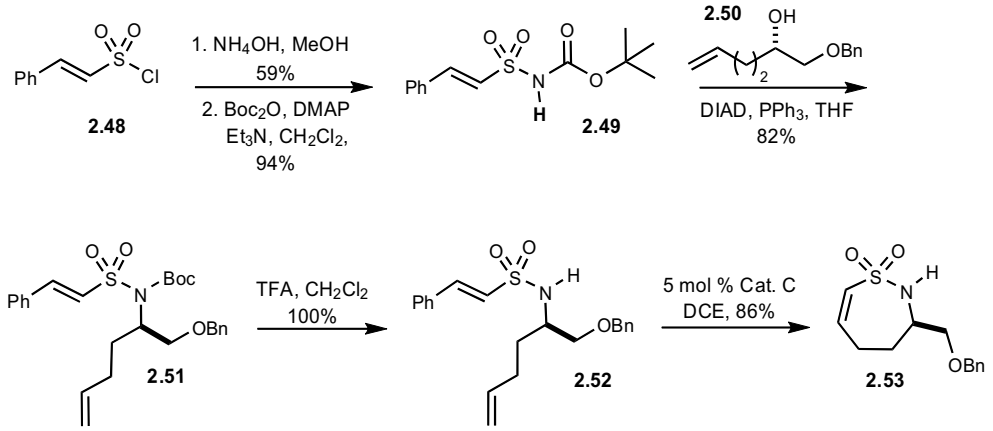



## 2.4 Synthesis of Seven-Membered Ring Vinylic Sultams

The RCM strategy utilized for the facile assembly of six-membered ring sultam scaffolds described in this chapter has prompted our efforts into extending this methodology for the construction of seven-membered ring vinylic sultams as outlined in Scheme 2.14. The synthesis of the desired seven-membered ring sultam **2.53** began with the multi-gram synthesis of styrylsulfonyl chloride (**2.48**) according to Culbertson and coworkers.[28] Conversion of **2.48** into the respective styrylsulfonamide under basic conditions with $NH_4OH$, followed by Boc-protection with $Boc_2O$,[3] afforded sufamoyl carbamate **2.49** in 94% yield. Mitsunobu alkylation with chiral, nonracemic alcohol **2.50**[29] in the presence of $PPh_3$ and DIAD in THF at room temperature provided chiral sulfonamide **2.51** in good yield (82%). Boc-group removal utilizing TFA in $CH_2Cl_2$ at room temperature afforded sulfonamide **2.52** in

quantitative yield. Facile RCM with 5 mol % of Grubbs second generation catalyst (Cat. C) in refluxing DCE afforded seven-membered ring vinylic sultam **2.53** in a good 86% yield. This new scaffold will be subjected to a variety of diversification reactions in the near future.

**Scheme 2.14**




## Conclusions

We have successfully synthesized a variety of sultam scaffolds in multi-gram quantities taking advantage of allyl sulfonyl chloride as the "sulfur linchpin" and RCM as the cyclization event. We have also demonstrated the chemical versatility offered by these scaffolds through a variety of diversification reactions utilizing solution-phase protocols. In addition, the use of ROMP-derived reagents developed in our laboratories has proved advantageous for the generation of sultam libraries using filtration as the sole method of purification. Using this developed synthetic approach, six-membered sultams with different groups around the periphery have been easily access in a concise manner and in excellent yields. Biological evaluation

of these novel sultams is currently in progress and is expected to contribute to drug discovery.

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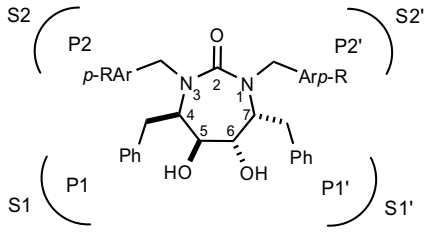
# Chapter 3

*Ring-Closing Metathesis Approaches to Symmetric and Unsymmetric Sulfamide Analogs of DMP 323 and N-hydroxy Cyclic Sulfamides*

As part of our efforts to synthesize different sulfur heterocycles as promising pharmacological agents, we considered the potential of utilizing the ring-closing metathesis reaction as the key cyclization step for the synthesis of symmetric and unsymmetric sulfamide analogs of the HIV protease inhibitor DMP 323 (Figure 3.1). It has been shown in the introductory chapter, (Chapter 1) that the RCM reaction can provide seven-membered rings in excellent yields. Moreover, a concise route that can afford these analogs and display inhibitory activity with improved pharmacokinetics seemed very attractive to our group. We therefore intended to explore an RCM approach to synthesize sulfamide analogs of DMP 323 in a more concise manner, where the final products can be obtained in good to excellent yields via a much shorter route compared to the one outlined in Scheme 1.49 (Chapter 1) by Hallberg and coworkers.[1] Presented in this chapter is our achievements towards the described symmetric and unsymmetric sulfur analogs of DMP 323. RCM efforts towards *N*-hydroxy cyclic sultams as potential MMP inhibitors will also be discussed.

**Figure 1** *Cyclic urea DMP 323*



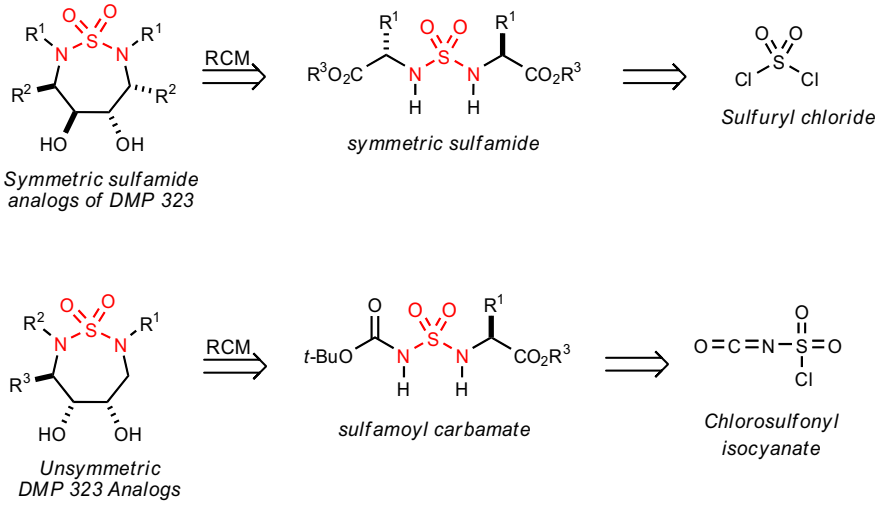

**DMP 323**
**R = $CH_2OH$**

## 3.1 Introduction of Sulfur Linchpins Using $SO_2Cl_2$ and CSI

Our interest in sulfamides and related analogs has led us to develop an RCM approach for the synthesis of symmetric and unsymmetric sulfamide analogs of DMP

323 (Figure 3.1). This strategy stems from our previous success to access symmetric and unsymmetric cyclic sulfamide peptidomimetics via a concise RCM strategy.[2] The developed strategy makes use of the reagents sulfuryl chloride ($SO_2Cl_2$, Scheme 3.1) and chlorosulfonyl isocyanate (CSI, Scheme 3.1) as sulfur linchpins to produce the respective symmetric sulfamide and unsymmetric sulfamoyl carbamate building blocks that could be easily accessed via a three-component coupling protocol. The sulfamide and sulfamoyl carbamate obtained can be further functionalized via Mitsunobu alkylation and simple alkylation procedures. Further transformations will lead to the desired differentiated sulfamide analogs of DMP 323.

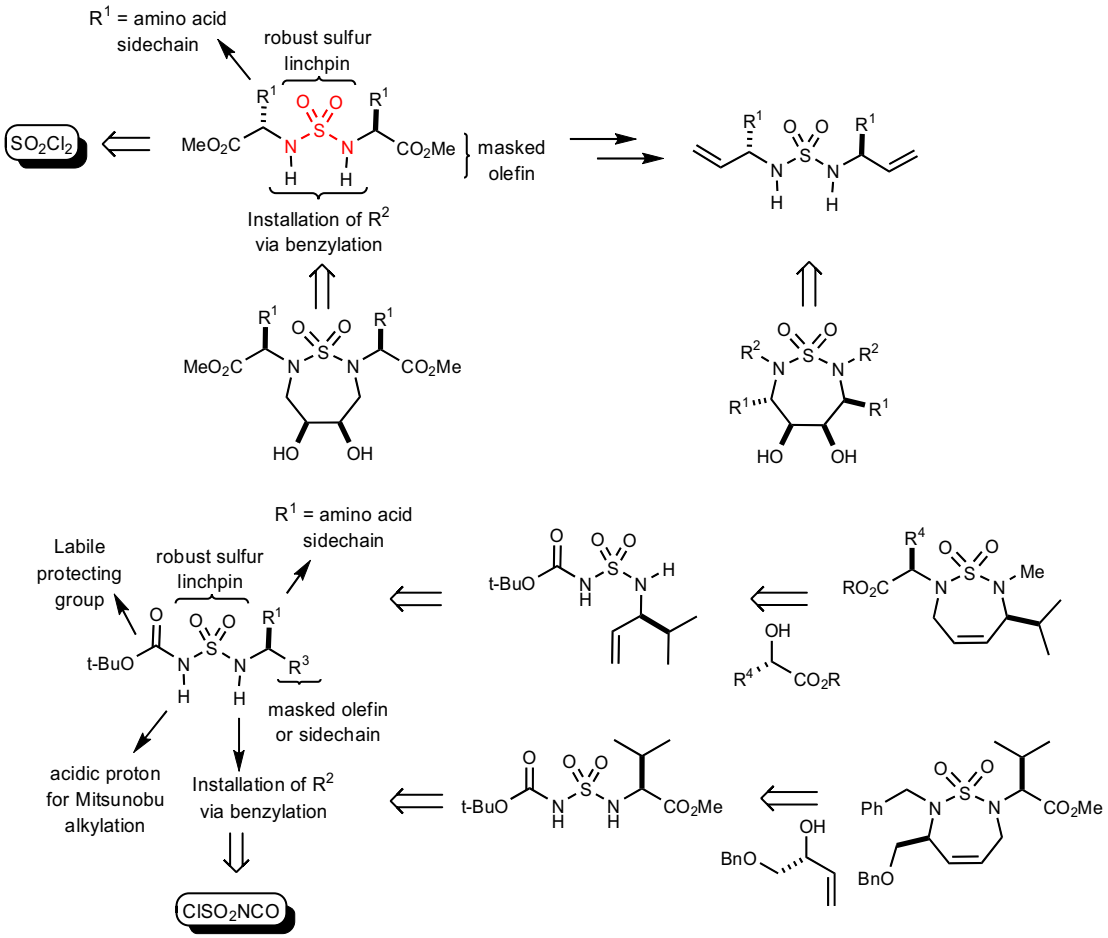
**Scheme 3.1**




Overall, the strengths of these approaches lie in the ability to (1) exploit the versatility of both sulfamide and sulfamoyl carbamate building blocks to effectively serve as "robust *S*-linchpins" to allow a number of simple but powerful transformations to occur, (2) incorporate simple ester groups (Scheme 3.2) as latent or masked olefins for subsequent cyclization using the RCM reaction, (3) effective

use of the Mitsunobu reaction with enantiopure alcohols (Scheme 3.2) and simple alkylation reaction protocols to selectively install the desired side chain groups at the P1/P1' and P2/P2' periphery (Figure 3.1) of the cyclic sulfamides. This strategy was developed to allow for strategic placement of side-chain groups in each of the P1/P1'/P2/P2' residues of the cyclic sulfamide with the ultimate goal of occupying the active site of HIV protease. The combination of the *S*-linchpin with non-racemic chiral building blocks (Scheme 3.2) will be vital for the success of the developed route.

**Scheme 3.2**

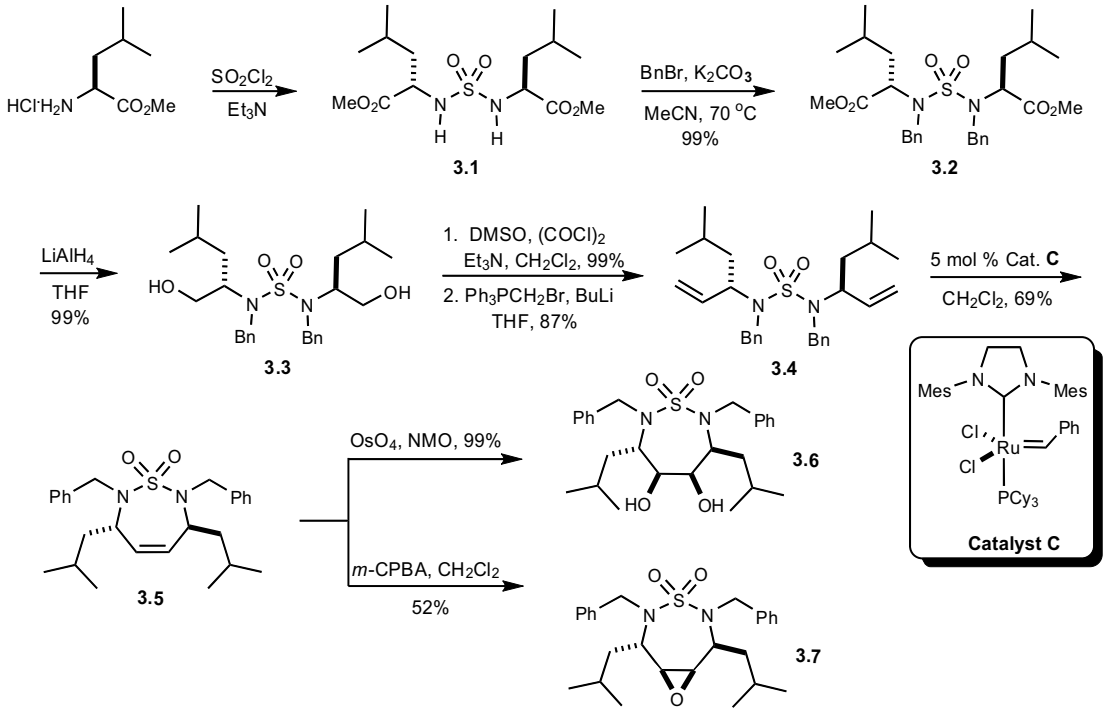


### 3.2 RCM Route Towards Symmetric and Unsymmetric Cyclic Sulfamides

We initiated our study with the synthesis of $C_2$-symmetric sulfamide analogs of DMP 323. Our new route towards cyclic $C_2$-symmetric sulfamides commenced with a two-directional chain synthesis to obtain sulfamide **3.1**. Sulfamide **3.1** was synthesized by the coupling reaction of L-leucine amino ester with sulfuryl chloride ($SO_2Cl_2$) under basic conditions as previously reported in our group (Scheme 3.3).[2] Dialkylation of leucine-derived sulfamide **3.1** under standard conditions using BnBr in the presence of $K_2CO_3$ in MeCN at 70 °C gave the corresponding bis-benzylated sulfamide **3.2** in excellent yield (99%).[3] The homotopic ester moieties in $C_2$-symmetric sulfamide **3.2** were then converted to terminal olefins via a three-step protocol to afford bis-olefin **3.4**. Subsequent reduction of the esters present in sulfamide **3.2** with $LiAlH_4$ cleanly produced diol **3.3** in quantitative yield (100%). Conversion of the diol moieties in **3.3** into the respective bis-aldehyde was achieved in excellent yield (99%) via Swern oxidation. This bis-aldehyde was carried on immediately without further purification to bis-Wittig olefination with $PPh_3CH_2Br$ in the presence of BuLi to generate diene sulfamide **3.4**. The efficiency of this three-step protocol further demonstrates the robust nature of the sulfamide group as it withstood a variety of reaction conditions to cleanly afford diene **3.4**. Ring-closing metathesis with 5 mol% of Grubbs second generation catalyst $[(ImesH_2)(PCy_3)(Cl)_2\text{-}Ru{=}CHPh]$[4] in refluxing $CH_2Cl_2$ proceeded smoothly to generate cyclic sulfamide **3.5** in 69% yield. Dihydroxylation of cyclic $C_2$-symmetric sulfamide **3.5** bearing homotopic olefinic faces was achieved by treatment with catalytic amounts of $OsO_4$ (3 mol %) in

the presence of NMO (1.2 equiv.) to produce cyclic sulfamide diol **3.6** in excellent yield (99%). Alternatively, epoxidation of sulfamide **3.5** using 4 equiv. of *m*-CPBA successfully gave the epoxy sulfamide **3.7** in modest yield (52%, unoptimized).

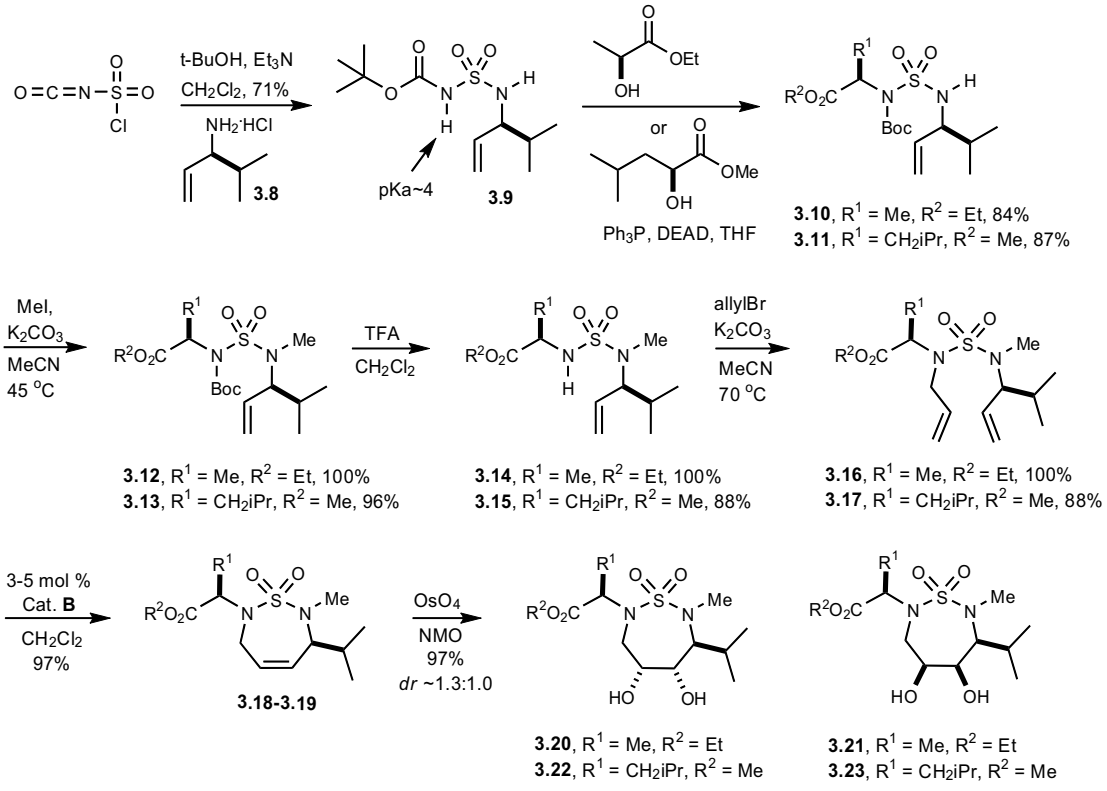
**Scheme 3.3**




Our synthetic approach was then applied to unsymmetric cyclic sulfamides bearing stereogenic centers in both the P1/P1' and P2/P2' positions. This synthetic pathway was successfully achieved as outlined in Scheme 3.4. Initially, a three-component coupling reaction with *tert*-butyl alcohol, chlorosulfonyl isocyanate (CSI), and the valine-derived allylic amine salt **3.8**[5,6] under basic conditions gave the corresponding sulfamoyl carbamate **3.9** in 71% yield (Scheme 3.4). This building block, first developed by Montero and co-workers,[7] contains two nucleophilic N-H sites of varying pKa's that can be chemoselectively differentiated (eg. Mitsunobu

alkylation). Thus, sulfamoyl carbamate **3.9** was first alkylated at the carbamate N-H (pKa ~ 4) under Mitsunobu conditions using $PPh_3$ and DEAD in THF at rt with either ethyl lactate or 2-hydroxy-4-methylpentanoic acid methyl ester to produce **3.10** and **3.11** in good yields (84% and 87%, respectively). Methylation of the remaining sulfamide N-H site in sulfamide **3.10** and **3.11** using MeI and $K_2CO_3$ in MeCN afforded sulfamides **3.12** and **3.13** in excellent yields (96-100%). Boc-removal under acidic conditions using TFA in $CH_2Cl_2$ at rt provided **3.14** and **3.15** in good to excellent yields (88-100%). Subsequent allylation of sulfamides **3.14** and **3.15** with allyl bromide and $K_2CO_3$ in MeCN at 70 °C generated the metathesis precursors **3.16**

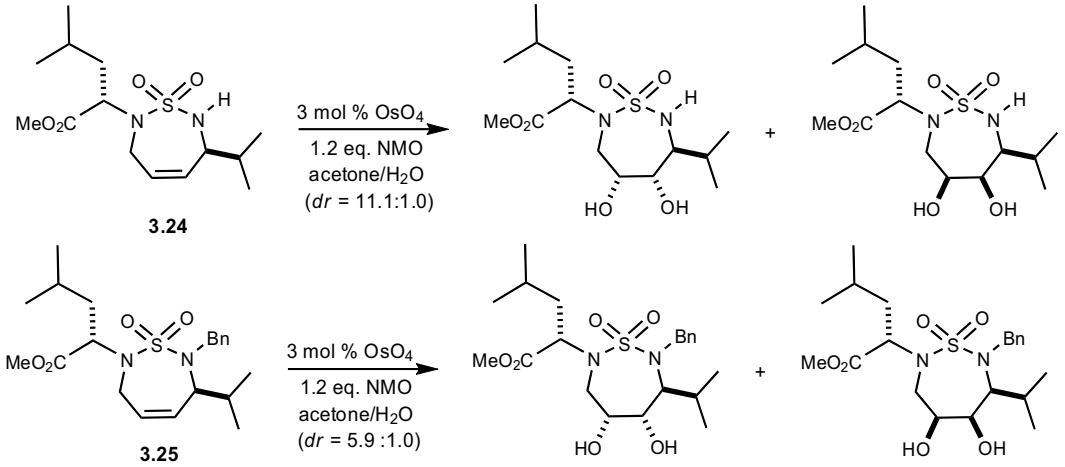
**Scheme 3.4**



and **3.17** in synthetically attractive yields (88-100%). RCM reaction with 3-5 mol% of the first generation Grubbs catalyst $[(PCy_3)_2(Cl)_2Ru=CHPh]$[8] under refluxing $CH_2Cl_2$ afforded the differentiated unsymmetric cyclic sulfamides **3.18** and **3.19** in nearly quantitative yields (97%). Surprisingly, dihydroxylation of sulfamides **3.18** and **3.19** occurred with little stereoselectivity to yield an approximate 1.3:1 diastereomeric mixture of diols **3.20** and **3.21** and **3.22** and **3.23** respectively in a combined yield of 97%.

Previous work in our group has demonstrated that osmium-mediated dihydroxylation of seven membered ring sulfamide systems that are structurally similar to sulfamide **3.19** ($R^1 = CH_2iPr$, $R^2 = Me$), occurred with good diastereofacial selectivity (dr = 5.9-11:1, Figure 3.2).[9] In this previous study, it was found that the nature of the *N*-substituent adjacent to the isopropyl sidechain has a considerable influence on the diastereoselectivity of the diol. In the two cyclic sulfamide cases studied, when R=H (**3.24**) good diastereoselectivity was observed in the product (dr = 11.1:1.0). However, the selectivity was significantly diminished in the dihydroxylation of the benzyl substituted sulfamide **3.25** (dr = 5.9:1.0). When taken collectively, it appears that *N*-substitution on the cyclic sulfamide has a significant effect on the diastereoselectivity of the dihydroxylation. Preliminary molecular modeling experiments suggest that *N*-substitution effects the orientation of the isopropyl group in cyclic sulfamide **3.25**, leading to a decrease in diastereoselectivity.

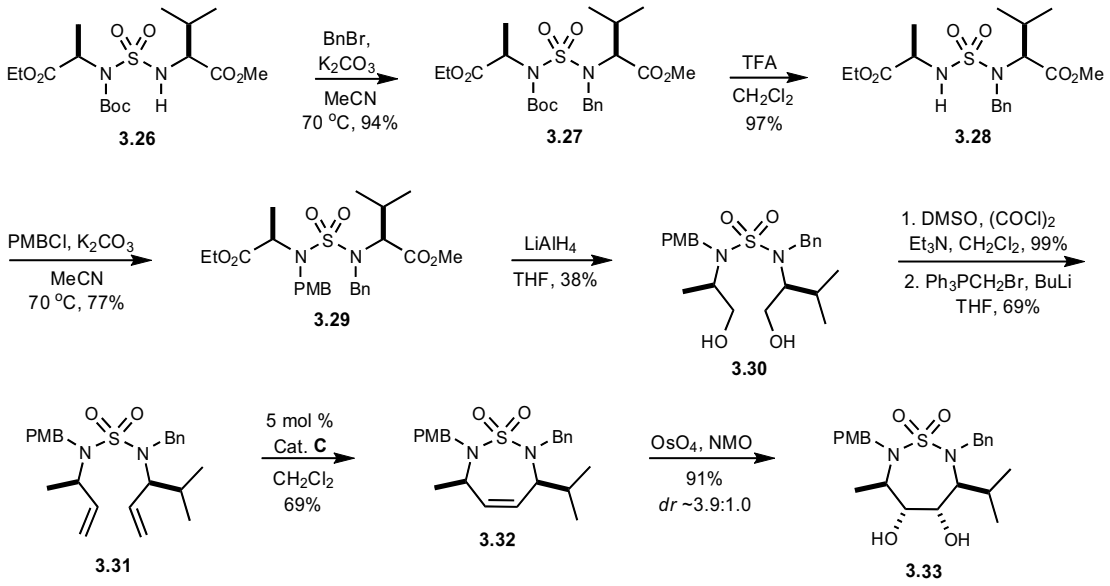
**Figure 3.2** *Diastereoselectivities obtained in the dihydroxylation step*




The methods outlined in Schemes 3.3 and 3.4 were exploited further in the synthesis of an unsymmetric sulfamide bearing differentiated P1/P1'/P2/P2' regions as shown in Scheme 3.5. Thus, benzylation of our previously reported unsymmetric sulfamoyl carbamate **3.26**[2] under standard benzylation conditions (BnBr, $K_2CO_3$, MeCN, 70 °C) provided benzylated sulfamide **3.27** in excellent yield (94%). Removal of the Boc group under acidic conditions (TFA, $CH_2Cl_2$) proceeded in excellent yield (97%) allowing for further diversification at the newly formed free N-H in sulfamide **3.28**. Installation of a PMB group under basic alkylating conditions with PMBCl and $K_2CO_3$ in MeCN at 70 °C proceeded without incident to generate sulfamide **3.29** in good yield (77%). Sulfamide **3.29** was then subjected to a two-directional chain synthesis employing the aforementioned three-step transformation of both ester groups into the corresponding olefinic groups for further RCM. Thus, reduction of the ester moieties with LAH (38%), followed by oxidation of the bis-alcohol to the respective bis-aldehyde via Swern oxidation (99%), and conversion to

the bis-olefin via Wittig olefination ($Ph_3PCH_2Br$ and BuLi) produced the metathesis precursor **3.31** in good yield (69%). RCM with 5 mol% $(ImesH_2)(PCy_3)(Cl)_2R{=}CHPh$ proceeded smoothly to yield the unsymmetric sulfamide **3.32** in good yields (69%) bearing differentiated lipophilic side-chains that occupy the P1(Me), P1' (iPr), P2 (PMB), and P2' (Bn) positions. Final osmium-mediated dihydroxylation afforded the sulfamide diol **3.33** in excellent yield (91%), but with only modest diastereoselectivity (dr = 3.9:1).

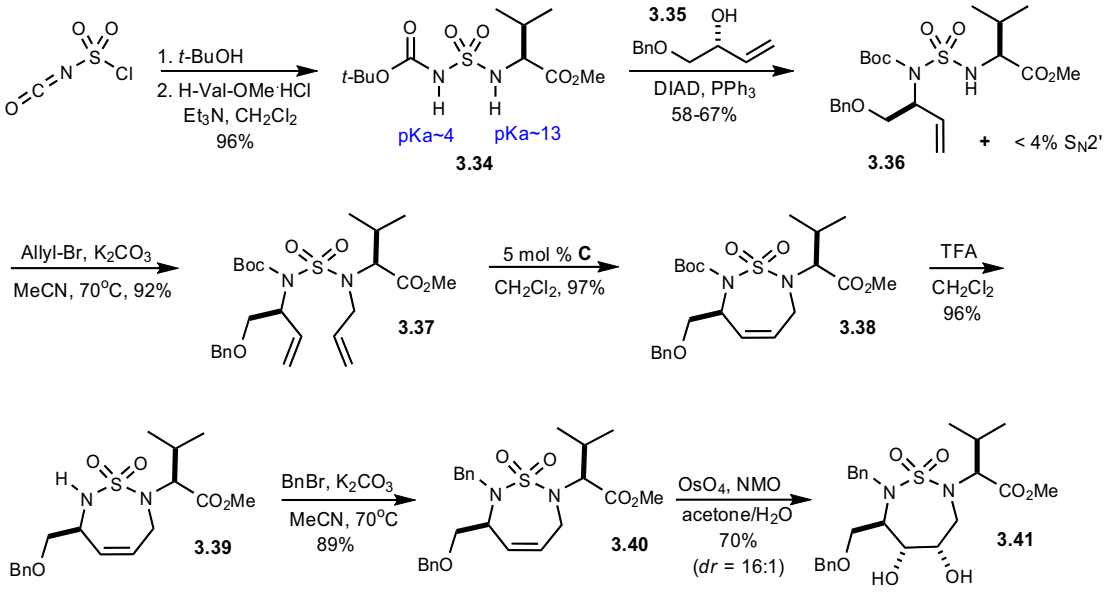
**Scheme 3.5**




The final approach that we investigated is outlined in Scheme 3.6. This new strategy employs the Mitsunobu reaction to install the stereogenic center occupying the P1 position. Initial three-component coupling with *tert*-butyl alcohol, CSI and L-valine methyl ester afforded sulfamide **3.34**, which now contains two N-H sites with different pKa's that can be used for selective alkylation to install the desired substituents at the periphery of the cyclic sulfamide. Thus, Mitsunobu alkylation of

sulfamide **3.34**[2] at the most acidic N-H site (pKa ~ 4) was possible with the readily prepared, chiral, nonracemic secondary allylic alcohol **3.35**, derived from the condensation of trimethyl sulfonium ylide with (*R*)-benzyl protected glycidol,[10] in the presence of DIAD and $PPh_3$ in THF at rt to generate sulfamide **3.36** in 67% yield. It is important to note that the Mitsunobu product primarily originated from the desired $S_N2$ pathway rather than the competing $S_N2'$ route. The solvent system chosen for this transformation had minor influence upon the ratio of the two observed products as seen in the following examples: THF (9.3:1 **3.36**:$S_N2'$), $CH_2Cl_2$ (8:1, **3.36**:$S_N2'$) and benzene (>10:1, **3.36**:$S_N2'$) as determined by $^1H$ NMR integration of the crude reaction mixture. Allylation of sulfamide **3.36** using identical allylation conditions as described before (allyl-Br, $K_2CO_3$, MeCN, 70 °C) yielded sulfamide diene **3.37** in a 92% yield. RCM with 5 mol% of catalyst C produced the cyclic sulfamide **3.38** in excellent yield (96%). Removal of the Boc group with TFA in $CH_2Cl_2$ at rt (96%), and benzylation under the previously described conditions (BnBr, $K_2CO_3$, MeCN, 70 ° C) gave the desired cyclic sulfamide **3.40** in good yield (89%). Finally, dihydroxylation with $OsO_4$ (6 mol %) afforded the differentiated sulfamide diol **3.41** in good yield (70%) and with high diastereoselectivity (dr = 16:1), with the major product tentatively assigned as the diastereomer resulting from dihydroxylation on the olefinic face opposite to the benzyloxymethyl group of the adjacent stereocenter.

**Scheme 3.6**



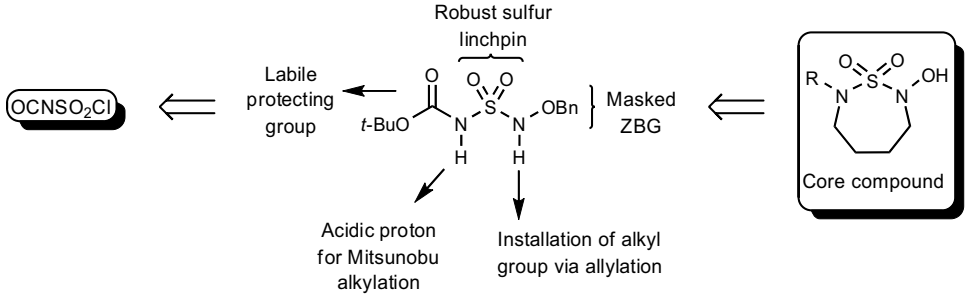

## 3.3 RCM Approach Towards *N*-Hydroxy Cyclic Sulfamides

The successful application of the RCM reaction for the construction of a variety of cyclic sulfamides containing different groups at the P1/P1' and P2/P2' positions has led us to investigate the generation of *N*-hydroxy cyclic sulfamides as potential MMP inhibitors via the same synthetic pathway developed in our group. As described in the introductory chapter (Chapter 1), matrix metalloproteinases (MMPs), also called matrixins, are zinc-containing enzymes that are involved in the remodeling and breakdown of extracellular matrix proteins.[11] Studies have revealed that overexpression of the MMPs can lead to a number of serious diseases such as arthritis and cancer.[12,13] To date, over 20 MMPs are known, all of which contain a zinc-binding group (ZBG) that is essential for inhibitory potency (Scheme 3.7).[14] However, it has not yet been possible to identify specific inhibitors for each of the

MMP enzymes. Therefore, the synthesis of *N*-hydroxy cyclic sulfamides as potential MMP inhibitors seems to be a viable goal.

Our efforts towards biologically active sulfur-containing compounds have led us to synthesize cyclic *N*-hydroxy sulfamides as potential MMP inhibitors. We reasoned that the synthesis of cyclic sulfamides will provide conformational restriction around the ZBG (in this case *N*-OH) which may increase the potency of these compounds towards MMP by promoting favorable enzyme/inhibitor interactions. The retrosynthetic pathway for the design of the conformationally constrained sulfamide inhibitors of MMP is shown in Scheme 3.7.

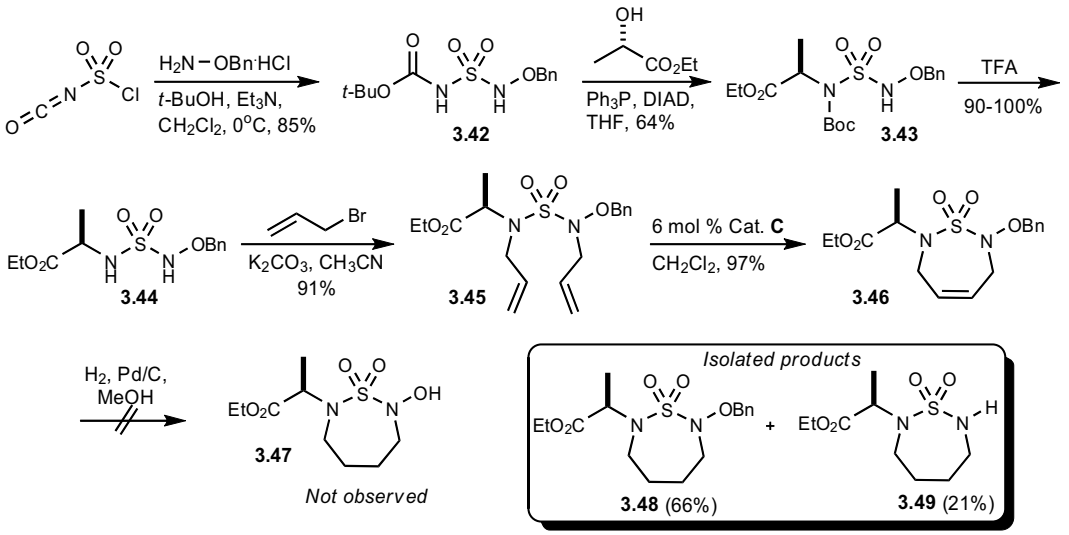
**Scheme 3.7**




The generation of the *N*-*O*-benzyl cyclic sulfamide **3.46** was achieved as outlined in Scheme 3.8,[15] beginning with a three-component coupling reaction with *tert*-butyl alcohol, CSI and *O*-benzyl hydroxylamine hydrochloride in $CH_2Cl_2$ under basic conditions ($Et_3N$) at 0 °C to afford sulfamide **3.42** in good yield (85%). Mitsunobu alkylation with ethyl lactate, $PPh_3$ and DIAD in THF at rt afforded chiral sulfamide **3.43** in good yield (64%). Removal of the Boc group under acidic conditions (TFA, $CH_2Cl_2$, rt) occurred in excellent yields (90-100%) to afford sulfamide **3.44**, followed by simultaneous allylation at the two N-H sites under

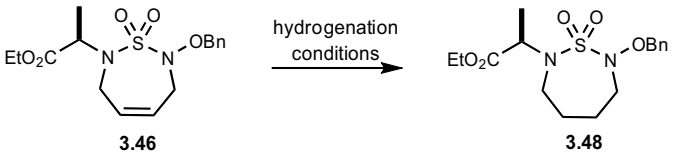
standard conditions (allyl-Br, $K_2CO_3$, MeCN, 70 °C) to provide diene **3.45** in a 91% yield. RCM with 6 mol % of catalyst C in refluxing $CH_2Cl_2$ proceeded smoothly to afford cyclic sulfamide **3.46** in excellent yield (97%). Finally, hydrogenation was attempted in order to obtain *N*-hydroxy sulfamide **3.47**. Initial efforts to obtain **3.47** under hydrogenation conditions ($H_2$, Pd/C, MeOH) were unsuccessful. Instead of affording the desired product **3.47**, a separable mixture of **3.48** (66%) and **3.49** (21%) was isolated.

**Scheme 3.8**




Two hydrogenation conditions were employed and the results are listed in table 3.1. Hydrogenation of cyclic sulfamide **3.46** using 5 mol % of Pd/C in EtOAc gave exclusively sulfamide **3.48** (entry 1, Table 3.1). Similar results were obtained when performing the reaction under microwave conditions in the presence of ammonium formate ($HCO_2^-NH_4^+$)[16] (entry 2, Table 3.1).

**Table 3.1** *Results obtained for the hydrogenation reaction*




3.46 3.48

| Entry | Conditions | % yield |
|---|---|---|
| 1 | $H_2$, 5% Pd/C, EtOAc, rt | 67 |
| 2 | $HCO_2^-NH_4^+$, μω | 71 |

Unfortunately, all the hydrogenation conditions employed failed to provide the desired *N*-hydroxy cyclic sulfamide **3.47**. Utilization of other reagents such as $TiCl_4$[17] will be explored in future efforts.

**Conclusions**

We have successfully synthesized a variety of symmetric and unsymmetric cyclic sulfamides with varied substitution in their P1/P1' and P2/P2' periphery. These syntheses have been accomplished using CSI or $SO_2Cl_2$ to generate the 'robust S-linchpins' in combination with Mitsunobu alkylations, simple alkylations, RCM, and diastereoselective dihydroxylations. This synthetic protocol proved useful for the synthesis of *N*-hydroxy cyclic sulfamides. Using this developed synthetic approach, seven-membered sulfamides with different groups around the periphery can be easily accessed in a concise manner and in excellent yields. Biological evaluation of these novel sulfamides is currently in progress and is expected to contribute to drug discovery.

**References for Chapter 3:**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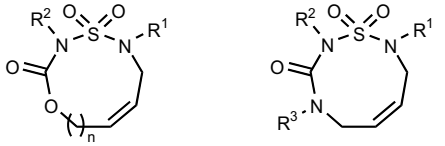
# Chapter 4:

*Ring-Closing Metathesis Approaches to the Synthesis of Cyclic Sulfamoyl Carbamates and Sulfamoyl Ureas*

## 4.1 Sulfamoyl Carbamates and Sulfamoyl Ureas

The recent growth of high-throughput screening for biologically active agents has increased the demand for the development of diverse libraries of synthetic compounds.[1-3] A growing area in combinatorial chemistry[4-8] is the generation of novel scaffolds that are extremely advantageous from both a chemical and a biological point of view.[9-13] The ability of the sulfonamide moiety, and related analogs, to serve as non-hydrolyzable amide surrogates has opened the door for their use as key functional groups in the development of new scaffolds. A number of compounds based on this premise have been developed including, biologically active sulfonamides,[14-16] sulfamides,[17-19] sulfamoyl carbamates,[20-22] sulfahydantoins,[23] and sulfamoyl ureas.[24-27] Recently, novel libraries based on sulfonamide,[28-32] sulfamoyl urea,[33] sulfahydantoin,[34-35] and sulfamide[36] scaffolds have been reported. Our interest in the development of new routes to access both phosphorus and sulfur-containing heterocycles (*P*- and *S*-heterocycles)[37] leads us to herein report a ring-closing metathesis (RCM) approach[37-41] to a diverse set of cyclic sulfamoyl carbamates and cyclic sulfamoyl ureas described in Figure 4.1.

**Figure 4.1** *Cyclic sulfamoyl carbamates and cyclic sulfamoyl ureas of interest*



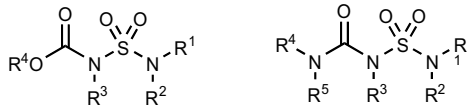

*Cyclic sulfamoyl carbamate*

*Cyclic sulfamoyl urea*

These compounds represent novel scaffolds possessing multiple points of diversity from which to produce combinatorial libraries, with the ultimate goal of biological screening.

Sulfamoyl carbamates of general structure shown in Figure 4.2 have been primarily used as important synthetic intermediates in the generation of unsymmetric sulfamides[37,42-43] and sulfahydantoins.[44] Their popularity originates from their ease of synthesis utilizing the previously mentioned 3-component coupling with chlorosulfonyl isocyanate (CSI), and facile functionalization by standard alkylation and Mitsunobu alkylation[45-46] resulting in the facile production of linear sulfamoyl carbamates,[47-50] sulfahydantoins,[44] and linear[44,19] and cyclic sulfamides.[37,42-43]

**Figure 4.2** *General structure of linear sulfamoyl carbamates and ureas*




As previously described in the introductory chapter (Chapter 1) sulfamoyl carbamates and sulfamoyl ureas have been studied as acyl-CoA:cholesterol O-acyl-transferase (ACAT) inhibitors.[22] However, reports of cyclic sulfamoyl carbamates are limited, and no examples of cyclic sulfamoyl carbamates of general structure shown in Figure 4.1 have appeared in the literature.

Sulfamoyl ureas (Figure 4.2) have also been shown to be biologically active.[22-27, 51-52] Large libraries of linear sulfamoyl ureas have been synthesized from the 3-component coupling of two amine nucleophiles and CSI. The chemical features of the sulfamoyl urea group are different from that of a sulfamoyl carbamate. Indeed,

the higher pKa of the urea N-H (pKa >10), compared to the carbamate N-H (pKa ~ 4), has hindered efforts to alkylate the urea N-H using the Mitsunobu reaction. Thus, derivatization of these compounds has previously fallen solely to base-promoted alkylation. Despite their importance as biological targets, cyclic sulfamoyl ureas have been largely unexplored.

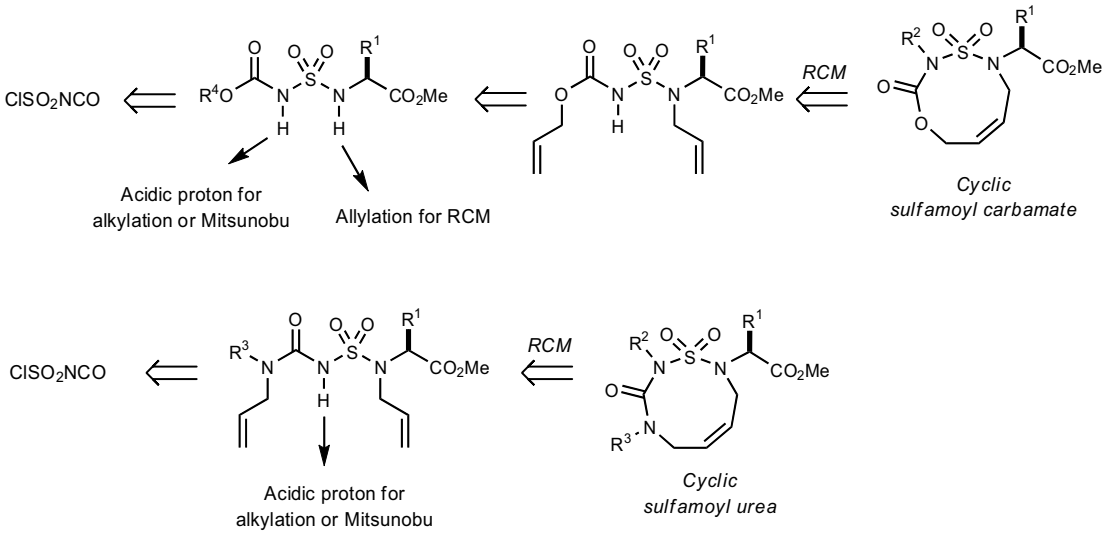
The emergence of ring-closing olefin metathesis (RCM)[53-59] over the last decade has fundamentally changed the method of generating both carbocyclic and heterocyclic targets.[58-59] Specifically, RCM has become an important and extremely useful transformation for the facile construction of small-, medium-, and large ring-containing systems.[58-60] When coupled with the versatile nature of both sulfamoyl carbamates and sulfamoyl ureas, several factors provided impetus for this investigation, including: (1) the ease of synthesis and analog generation in both sulfamoyl carbamate and urea classes, (2) the convenience of using RCM to generate cyclic structures, (3) the ability of both sulfamoyl carbamate and urea moieties to serve as surrogates for sulfamide or urea groups present in known biologically active systems, and (4) the correlation to the known biological activities of linear sulfamoyl carbamates and ureas.

### 4.2. RCM Approaches Toward Cyclic Sulfamoyl Ureas and Cyclic Sulfamoyl Carbamates

Previously, we have utilized sulfamoyl carbamate building blocks as synthetically valuable starting materials to generate a variety of unsymmetrical cyclic sulfamides related to the potent HIV protease inhibitors DMP 323 and DMP 450.[43]

Our new route utilizes this functional group as the central 'linchpin' in an RCM methodology. The strength of this approach lies in the wide variety of 9- to 11-membered cyclic sulfamoyl carbamates (Figure 4.3) and sulfamoyl ureas (Figure 4.3) that can be accessed from the corresponding dienes. The focal points of this method include the ability to: (1) use 3-component coupling of CSI, allylic alcohols and allylic amines to synthesize asymmetric sulfamoyl carbamates and sulfamoyl ureas, (2) functionalize the sulfamoyl carbamate nitrogen via a Mitsunobu reaction, (3) utilize base-promoted alkylation or the Mitsunobu reaction to functionalize the sulfamoyl urea nitrogen, and (4) generate novel cyclic sulfamoyl carbamates and sulfamoyl ureas utilizing RCM.

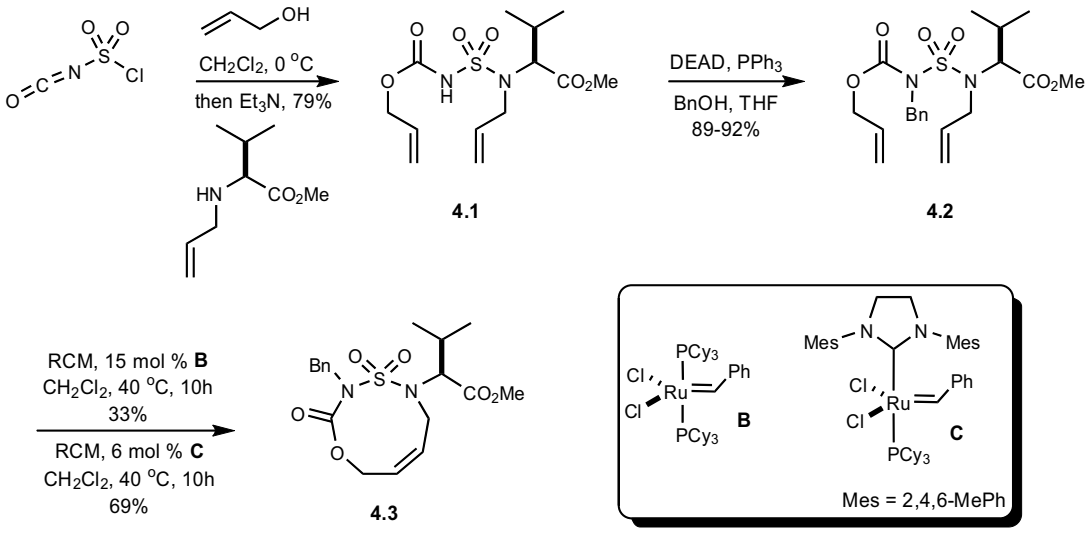
**Figure 4.3** *Synthetic approach towards cyclic sulfamoyl carbamates and ureas*




Our initial efforts began with the 3-component coupling of allyl alcohol, CSI, and *N*-allyl (L)-valine methyl ester to produce the corresponding sulfamoyl carbamate **4.1** (Scheme 4.1). Optimization of the reaction conditions led to the use of 1.2 equiv.

of $Et_3N$ to efficiently facilitate the formation of sulfamoyl carbamate **4.1** in 79% yield. Sulfahydantoin formation via intramolecular cyclization between the carbamate nitrogen and the ester group was thwarted under these optimized conditions. Next, it was synthetically desirable to functionalize the carbamate nitrogen in **4.1**. Though base-promoted alkylation of sulfamoyl carbamates with $K_2CO_3$ was a viable option, the Mitsunobu reaction was employed because of its versatility and to reduce possible hydantoin formation. Subjection of **4.1** to Mitsunobu conditions using benzyl alcohol (BnOH), DEAD and $PPh_3$ in THF at rt gave sulfamoyl carbamate **4.2** in excellent yields (89-92%).

**Scheme 4.1**

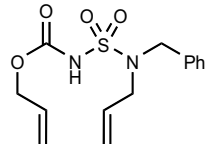
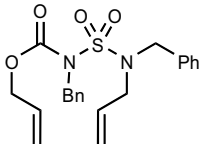
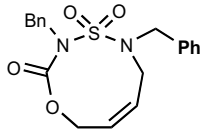
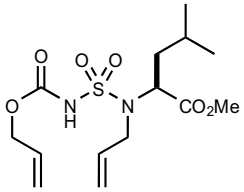
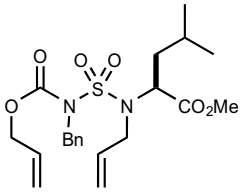
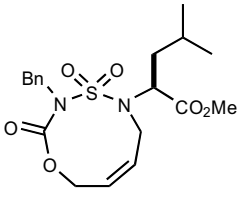
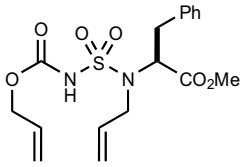
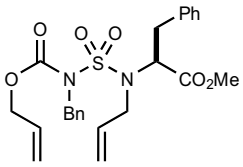
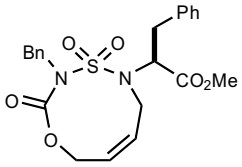



The initial attempts to cyclize diene **4.2** using Grubbs first generation catalyst $[(PCy_3)_2(Cl)_2Ru=CHPh]$ (cat-B)[61-63] in $CH_2Cl_2$ (0.009 M) resulted in the formation of 9-membered cyclic sulfamoyl carbamate **4.3** in only 33% yield, with a major byproduct (~30% yield) tentatively assigned as the dimer arising from cross-metathesis (X-MET). The difficulty in confirming such a product was the result of

carbamate C–N bond rotamers that are present in the cross metathesized product. Proton NMR experiments on these sulfamoyl carbamates conducted at 50 °C failed to overcome the rotational barrier. RCM using the more active second generation catalyst [$(IMesH_2)(PCy_3)(Cl)_2Ru$=CHPh] (cat-C)[69] in $CH_2Cl_2$ (0.009 M) resulted in the formation of the desired 9-membered cyclic sulfamoyl carbamate **4.3** in 69% overall yield, with no detectable dimer formation via X-MET. This newly formed sulfamoyl carbamate represents the first example of RCM on this class of compounds and highlights the potential for library production utilizing more elaborate alcohols at the initial coupling and subsequent Mitsunobu alkylation steps.

With a general route to cyclic sulfamoyl carbamates in hand, analogous cyclic sulfamoyl carbamates were synthesized using benzylamine and other (L)-amino esters as represented in Table 4.1. Coupling with CSI and allyl alcohol afforded sulfamoyl carbamates **4.4-4.6** in good yields (85-90%). Benzylation of sulfamoyl carbamates **4.4-4.6** via the Mitsunobu reaction with BnOH, DEAD and $PPh_3$ in THF afforded metathesis precursors **4.7-4.9** in 81-92% yields. RCM with 6 mol% of cat-C gave cyclic sulfamoyl carbamates **4.10-4.12** in modest yields (40-52%). Removal of residual ruthenium was achieved using DMSO according to Georg.[65] Surprisingly, although these yields were marginal (40-52%), no X-MET dimer was observed, prompting us to further optimize the RCM reaction.

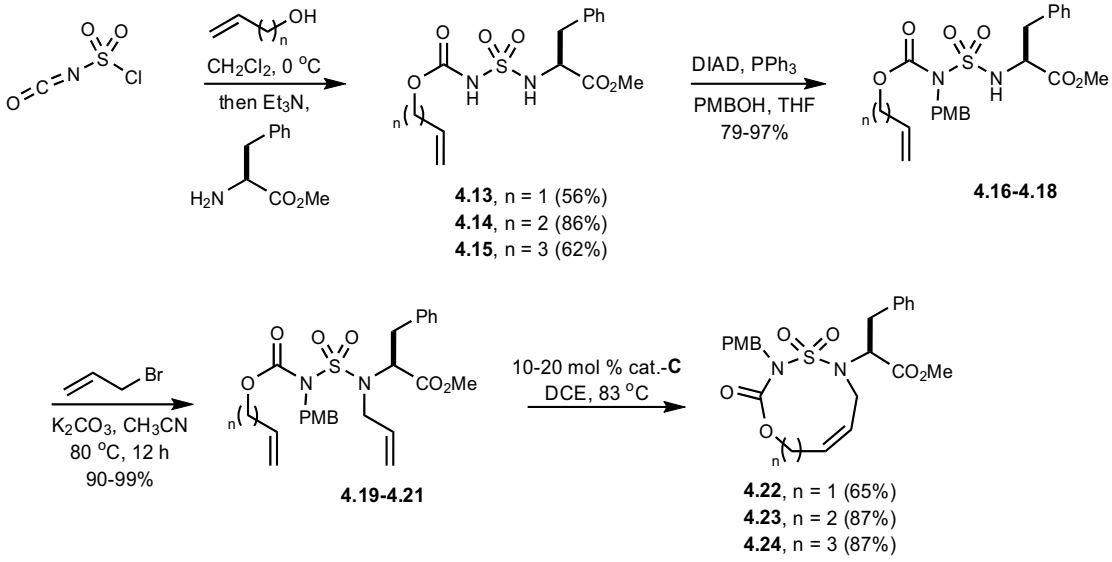
**Table 4.1:** *RCM route to 9-membered ring sulfamoyl carbamates*

| Entry | 3-component coupling product (% yield) | Mitsunobu product (% yield) | RCM Product (% yield) |
|---|---|---|---|
| 1 |  **4.4** (90%) |  **4.7** (92%) |  **4.10** (40%) |
| 2 |  **4.5** (85%) |  **4.8** (87%) |  **4.11** (51%) |
| 3 |  **4.6** (86%) |  **4.9** (81%) |  **4.12** (52%) |

In the second route shown in Scheme 4.2, the 3-component coupling reaction was carried out with various olefinic alcohols of varying chain length, CSI, and (L)-phenylalanine methyl ester to produce the corresponding sulfamoyl carbamates **4.13-4.15** in good yields (56-86%). The Mitsunobu reaction with PMBOH, DIAD and $PPh_3$ in THF was employed to regioselectively install the PMB moiety at the carbamate position (pKa ~ 4) in sulfamoyl carbamates **4.13-4.15** to afford PMB-

protected sulfamoyl carbamates **4.16-4.18** in good to excellent yields (79-97%). Allylation of the PMB-protected carbamates **4.16-4.18** under standard conditions (allyl bromide and $K_2CO_3$ in MeCN under reflux) produced RCM precursors **4.19-4.21** in high yields (90-99%). Subjection to RCM conditions using 10-20 mol % of cat-C in refluxing DCE (0.005 M) gave the corresponding 9-, 10-, and 11-membered cyclic sulfamoyl carbamates **4.22-4.24** in good yields (65-87%).

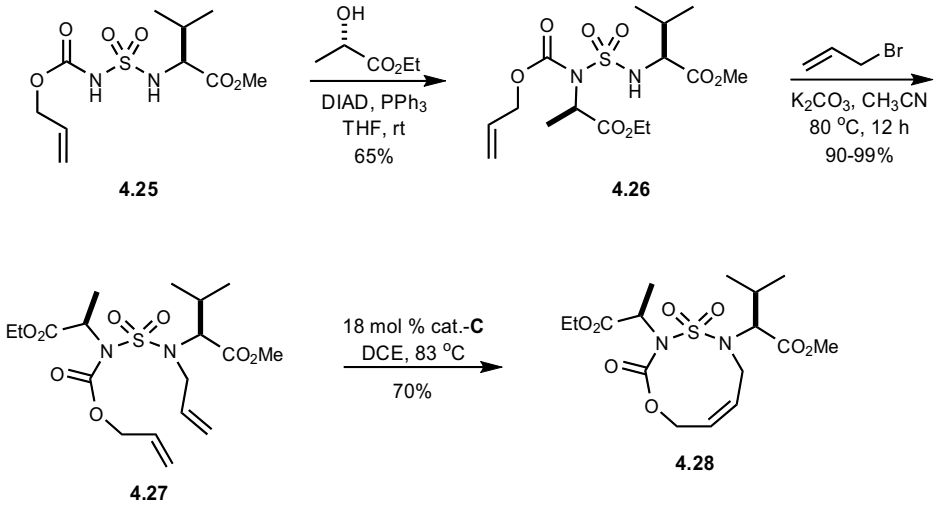
**Scheme 4.2**




The initial examples outlined in Schemes 4.1 and 4.2 utilized simple Mitsunobu benzylation to install diversity at the sulfamoyl carbamate. Installation of side chains bearing stereogenic centers, as previously shown in the synthesis of unsymmetric sulfamides,[42-43] were next pursued as outlined in Scheme 4.3. Thus, alkylation of sulfamoyl carbamate **4.25** with naturally occurring (S)-ethyl lactate under Mitsunobu conditions (DIAD, $PPh_3$ in THF, rt), generated alkylated sulfamoyl carbamate **4.26** in 65% yield. Simple allylation under standard conditions provided

diene **4.27** in good yield (68%), followed by RCM in refluxing DCE to afford cyclic sulfamoyl carbamate **4.28** in good yield (70%) containing both valine and alanine side chains at the periphery.

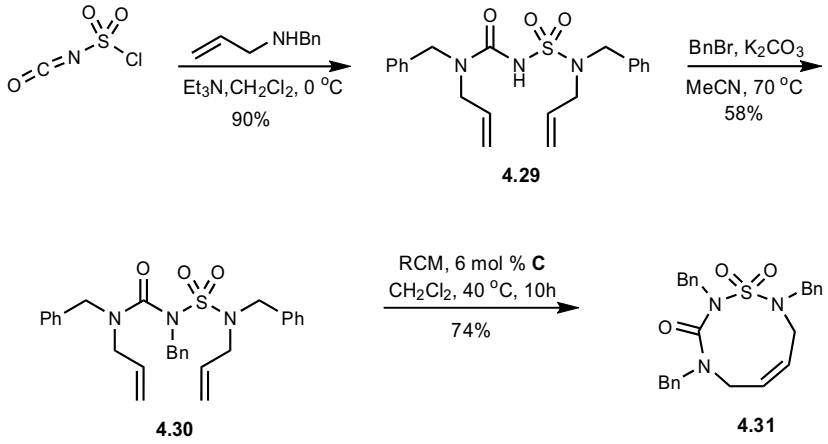
**Scheme 4.3**




Subsequent efforts were focused toward the exploration of a similar three-step protocol to generate 9-membered cyclic sulfamoyl ureas (Scheme 4.4). Benzylamine was chosen as the initial test substrate, due to potential problems with sulfahydantoin formation from the use of amino esters, *vide infra*. Coupling of 2 equiv. of benzylamine with CSI gave linear sulfamoyl urea **4.29** in 90% yield (Scheme 4.4). As with the sulfamoyl carbamates, functionalization of the urea nitrogen with a benzyl group was desirable. Unfortunately, sulfamoyl ureas were unable to undergo Mitsunobu benzylations under standard DEAD or DIAD conditions. Initial attempts at benzylation using DBU and NaH were found to be surprisingly ineffective despite literature precedent,[22] yielding no noticeable benzylated product. Utilizing our previous method to alkylate sulfamides (BnBr, $K_2CO_3$, MeCN) resulted in the

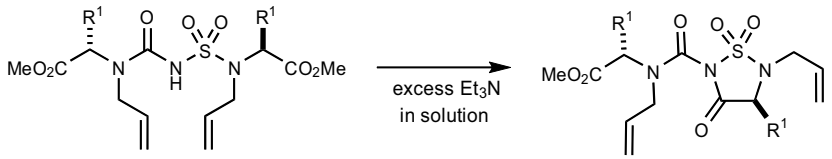
formation of benzylated sulfamoyl urea **4.30**, albeit in a modest 58% yield. RCM of **4.30** proved to be efficient as 6 mol% cat-C in $CH_2Cl_2$ (0.01 M) afforded 9-membered cyclic sulfamoyl urea **4.31** in 74% yield. Importantly, no product arising from X-MET was observed. This result represents the first known example of RCM on a sulfamoyl urea template, and opens opportunities to diversification strategies.

**Scheme 4.4**




With a method for the generation of cyclic sulfamoyl ureas in hand, the synthesis of sulfamoyl ureas utilizing allylated aminoesters was explored. Sulfahydantoin formation, arising from attack of the sulfamoyl urea nitrogen into the sulfamide amino ester forming hydantoin **4.35**, was of major concern (Scheme 4.5). Thus, our initial use of excess base in the initial 3-component coupling reaction generated sulfahydantoins **4.35-4.37** as a significant byproduct. In addition, the sulfamoyl ureas were found to cyclize the substrates to the sulfahydantoins **4.35-4.37** at rt with excess $Et_3N$ in solution and in small amounts during purification via column chromatography.

**Scheme 4.5**

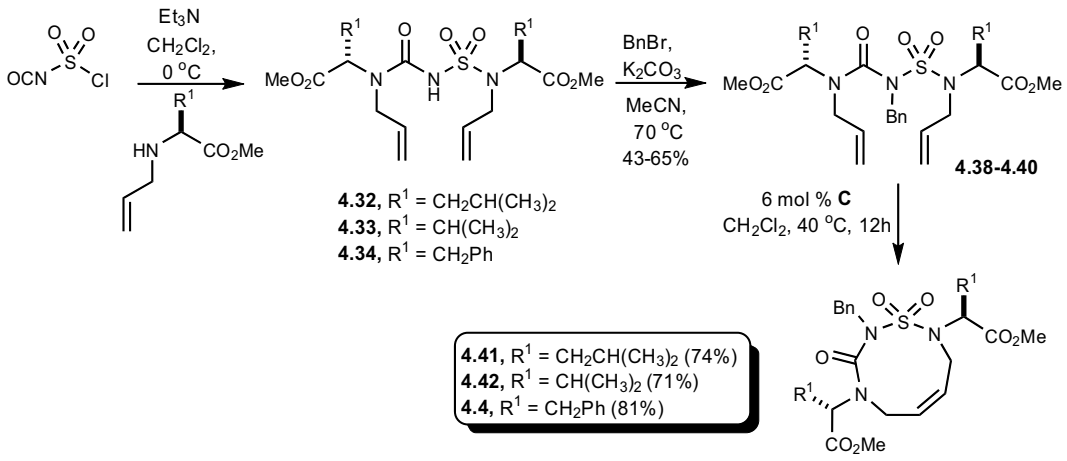



**4.32,** $R^1 = CH_2CH(CH_3)_2$
**4.33,** $R^1 = CH(CH_3)_2$
**4.34,** $R^1 = CH_2Ph$

**4.35-4.37**

Despite these concerns, our initial 3-component coupling reaction with a variety of allylated amino esters and CSI produced sulfamoyl ureas **4.32-4.34** in good overall yields (Scheme 4.6). Furthermore, optimal results were obtained with 1.2 equiv. of $Et_3N$ and 2.2 equiv. of the amino ester. Lowering the equivalents of the amino ester gave a complex mixture of product, sulfahydantoin and sulfamoyl chloride. For stability reasons, benzylation was therefore utilized as a means of both protection and functionalization. The standard $K_2CO_3$ promoted benzylation of **4.32-4.34** resulted in moderate yields of benzyl-protected RCM precursors **4.38-4.40** (43-65%).

**Scheme 4.6**



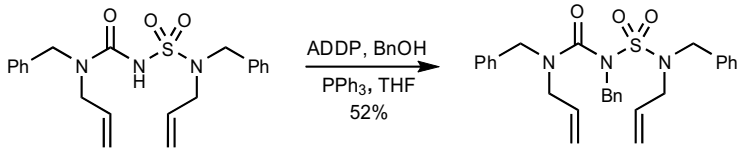

**4.32,** $R^1 = CH_2CH(CH_3)_2$
**4.33,** $R^1 = CH(CH_3)_2$
**4.34,** $R^1 = CH_2Ph$

**4.38-4.40**

**4.41,** $R^1 = CH_2CH(CH_3)_2$ (74%)
**4.42,** $R^1 = CH(CH_3)_2$ (71%)
**4.4,** $R^1 = CH_2Ph$ (81%)

Surprisingly, these conditions produced only minor amounts of the sulfahydantoin despite elevated temperatures, with no single entry yielding more than 5% of hydantoin byproduct. Metathesis of the amino ester-derived sulfamoyl ureas provided consistent results as treatment of dienes **4.38-4.40** with 6 mol% of cat-C afforded the desired cyclic sulfamoyl ureas **4.41-4.43** in good yields (71-81%). Importantly, no byproducts arising from X-MET were observed.

**Scheme 4.7**




**4.29** **4.30**

An alternate route to benzylation was sought in order to circumvent problems associated with generating benzylated sulfamoyl ureas. We felt that if a Mitsunobu reaction could be initiated at the sulfamoyl urea nitrogen, the potential for derivatization would greatly improve. The difficulty is encountered in the inability of the DEAD/$PPh_3$ complex to deprotonate the sulfamoyl ureas containing a less acidic N-H moiety. Mitsunobu reactions with higher pKa nucleophiles have been realized with the advent of 1,10-(azodicarbonyl) dipiperidine-tributylphosphine (ADDP)[66] as a more powerful DEAD equivalent. To test the efficacy of this method, benzylamine-derived sulfamoyl urea **4.29** was subjected to modified Mitsunobu conditions with ADDP, to afford benzylated sulfamoyl urea **4.30** in 52% yield (Scheme 4.7). To our knowledge, this is the first example of a Mitsunobu reaction using a sulfamoyl urea as the nucleophile. Though the yield was less than that obtained via standard alkylation

conditions, these results are encouraging. In addition to nitrogen protection, utilization of more elaborate nonracemic secondary alcohols will provide an excellent pathway for diversification of these sulfamoyl ureas.

**Conclusions**

We have described the first synthesis of both cyclic sulfamoyl carbamates and ureas utilizing the RCM reaction. This method represents an extension of our success with our recent sulfamide research and a new direction in the synthesis of novel *S*-heterocycles. Further research on sulfamoyl carbamates will focus on functionalization of the sulfamoyl carbamate nitrogen utilizing secondary allylic alcohols and amines in the 3-component coupling reaction to generate a variety of novel sulfamoyl carbamates and sulfamoyl ureas. In addition, the Mitsunbou reaction will be optimized and exploited as an important means to functionalize the sulfamoyl ureas. Biological screening and further refinement of these compounds will be pursued.

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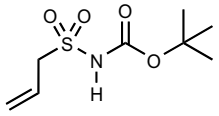
# Chapter 5

*Experimental*

All reactions were carried out in flame-dried glassware under argon. Toluene, THF, $Et_2O$, and $CH_2Cl_2$ were purified by passage through a purification system (Solv-Tek) employing activated $Al_2O_3$. $Et_3N$ was distilled from $CaH_2$. Flash column chromatography was performed with Merck silica gel (EM-9385-9, 230–400 mesh). Thin layer chromatography (TLC) was performed on silica gel 60F254 plates (EM-5715-7, Merck). All amino acid precursors were purchased from Advanced Chem Tech. $^1H$ and $^{13}C$ spectra were recorded in $CDCl_3$, MeOD or Acetone-$d_6$ on either a Bruker DRX-400 or a Bruker AM-500 spectrometer operating at 400/100 MHz and 500/125 MHz, respectively. High-resolution mass spectrometry (HRMS) and FAB spectra were obtained on a VG Instrument ZAB double-focusing mass spectrometer. Infrared data was obtained on a Nicolet 320 Fourier Transform Infrared Spectrophotometers. Melting points were obtained on a Thomas Hoover capillary melting point apparatus. Optical rotations were carried out on a Rudolph Automatic Polarimeter (AUTOPOL IV).

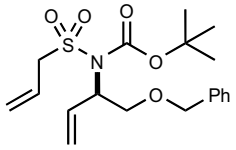
***tert*-butyl allylsulfonylcarbamate (2.3)**



To a solution of allyl sulfonamide **2.2** (500 mg, 4.13 mmol) in $CH_2Cl_2$ (5.2 mL) was added DMAP (50 mg, 0.41 mmol) and $Et_3N$ (459 mg, 4.53 mmol, 0.63 mL), followed by the dropwise addition of a solution of $Boc_2O$ (1.04 g, 4.75 mmol, 1.09 mL) in $CH_2Cl_2$ (8.3 mL) over 15 min. with stirring. The reaction was stirred at rt for 2.5 h after which the solvent was removed. To the crude mixture was added 1N HCl (25 mL) and the solution extracted with EtOAc (4 × 50 mL). The organic layer was washed with water (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Flash chromatography ($SiO_2$, 3:1 Heptane/EtOAc) afforded 851 mg (93%) of carbamate **2.3** as a yellow oil, which solidified to a crystalline yellow solid when left in the fridge. A small amount of the bisprotected product (46mg, 4%) was also isolated.

**Analytical data for 2.3:** TLC $R_f$ = 0.32 (1:1 Heptane/EtOAc); Mp = 43-45 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 6.97 (s, 1H, N-H), 5.90 (dddd, *J* = 17.4, 10.1, 7.4, 7.4 Hz, 1H), 5.49 (dd, *J* = 10.1, 1.0 Hz, 1H), 5.44 (dd, *J* = 17.0, 1.2 Hz, 1H), 4.11 (d, *J* = 7.4 Hz, 2H), 1.51 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 149.8, 124.8, 124.5, 84.1, 56.6, 27.7; FTIR (neat) 3242, 3094, 2982, 1742, 1641 $cm^{-1}$; HRMS $(M+Na)^+$ calcd for 244.0619, found 244.0610.

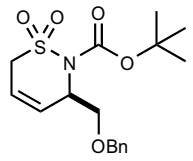
**(*R*)-*tert*-butyl allylsulfonyl(1-(benzyloxy)but-3-en-2-yl)carbamate (2.5)**




To a solution of allylic alcohol **2.4** (120 mg, 0.67 mmol), sulfamoyl carbamate **2.3** (149 mg, 0.67 mmol) and $PPh_3$ (228 mg, 0.87 mmol) in THF (13.4 mL) at rt was added DEAD (152 mg, 0.87 mmol, 0.14 mL) dropwise via syringe and the reaction stirred at rt until complete by TLC (usually < 1 h). Flash chromatography ($SiO_2$, 6:1 Hexane/EtOAc) afforded 219 mg (79%) of sulfonamide **2.5** as a yellow oil.

**Analytical data for 2.5:** TLC $R_f$ = 0.63 (2:1 Heptane/EtOAc); $[\alpha]_D^{25}$ = -9.70 (*c* = 1.125, $CHCl_3$) $^1$H NMR (400 MHz, $CDCl_3$) δ 7.27-7.19 (m, 5H), 5.92 (ddd, *J* = 17.2, 10.4, 6.5 Hz, 1H), 5.78 (dddd, *J* = 17.4, 10.1, 7.4, 7.4 Hz, 1H), 5.29 (dd, *J* = 9.9,1.0 Hz, 1H), 5.26 (dd, *J* = 17.1, 1.0 Hz, 1H), 5.23 (dd, *J* = 17.3, 1.0 Hz, 1H), 5.16 (dd, *J* = 10.4, 1.0 Hz, 1H), 4.96-4.90 (m, 1H), 4.52 (d, *J* = 11.8 Hz, 1H), 4.44 (d, *J* = 11.8 Hz, 1H), 4.16 (dd, *J* = 13.8, 7.6 Hz, 1H), 4.05 (dd, *J* = 13.7, 7.2 Hz, 1H), 3.84 (dd, *J* = 9.6, 8.8 Hz, 1H), 3.59 (dd, *J* = 9.7, 6.2 Hz, 1H), 1.43 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 151.0, 137.8, 134.0, 128.4, 127.7, 127.7, 124.7, 124.6, 118.5, 84.6, 73.0, 69.9, 59.3, 58.4, 28.0; FTIR (neat) 3088, 3030, 2978, 2930, 2868, 1726, 1639, 1497 $cm^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{19}H_{27}NO_5SNa$ 404.1508, found 404.1527.

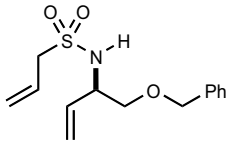
**1,2-thiazine-*N*-carboxylic acid-3,6-dihydro-(3*R*)-[(phenylmethoxy)methyl]-1,1-dimethylethyl ester-1,1-dioxide (2.6)**




To a solution of diene **2.5** (2.5 g, 6.55 mmol) in degassed toluene (655 mL) was added Grubbs second generation catalyst (Cat. **C**) (278 mg, 0.328 mmol) in one portion and the reaction heated at reflux for 3 h. The solvent was removed under reduced pressure, $CH_2Cl_2$ (50 mL) added and the residual ruthenium removed by addition of DMSO (1.28 g, 16.4 mmol, 1.16 mL) and stirring at rt for 12 h. Flash chromatography ($SiO_2$, 3:1 Hexane/EtOAc) afforded 2.0 g (87 %) of sultam **2.6** as an ivory solid.

**Analytical data for 2.6:** TLC $R_f$ = 0.33 (2:1 Heptane/EtOAc); Mp = 68-73 °C; $[\alpha]_D^{25}$ = + 120.4 (*c* = 0.955, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 5H), 6.01 (dddd, *J* = 10.8, 4.0, 1.6, 1.6 Hz, 1H), 5.78 (dddd, *J* = 10.4, 5.6, 2.8, 1.6 Hz, 1H), 5.27-5.24 (m, 1H), 4.55 (s, 2H), 3.92 (dddd, *J* = 16.4, 2.4, 2.4, 2.4 Hz, 1H), 3.78 (d, *J* = 6.4 Hz, 2H), 3.77-3.72 (m, 1H), 1.49 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 150.5, 137.8, 128.3, 127.6, 127.6, 126.8, 118.3, 84.6, 73.2, 70.7, 60.0, 50.3, 27.8; FTIR (neat) 2980, 2928, 2866, 1722, 1454 $cm^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{17}H_{23}NO_5SNa$ 376.1195, found 376.1212.

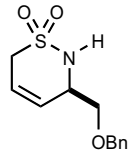
**(*R*)-*N*-(1-(benzyloxy)but-3-en-2-yl)prop-2-ene-1-sulfonamide (2.7)**




To a solution of diene **2.5** (330 mg, 0.87 mmol) in $CH_2Cl_2$ (3 mL) was added an excess of TFA (1 mL) dropwise via syringe and the reaction stirred at rt until all starting material was consumed (~30 min). The reaction mixture was quenched with 15 mL of saturated $NaHCO_3$ and extracted with $CH_2Cl_2$ (4 × 25 mL). The organic layers were combined, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. Flash chromatography ($SiO_2$, 3:1 Heptane/EtOAc) afforded 227 mg (93%) of sulfonamide **2.7** as a light yellow oil.

**Analytical data for 2.7:** TLC $R_f$ = 0.70 (1:1 Heptane/EtOAc); $[\alpha]_D^{25}$ = +4.65 (*c* = 0.817, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 5H), 5.90 (dddd, *J* = 17.2, 10.0, 7.2, 7.2 Hz, 1H), 5.83 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.38 (dd, *J* = 10.8, 1.0 Hz, 1H), 5.37 (dd, *J* = 17.2, 1.0 Hz, 1H), 5.35 (dd, *J* = 17.2, 1.0 Hz, 1H), 5.26 (dd, *J* = 10.4, 1.0 Hz, 1H), 4.81 (d, *J* = 7.5 Hz, 1H), 4.56 (d, *J* = 11.9 Hz, 1H), 4.51 (d, *J* = 11.8 Hz, 1H), 4.17-4.11 (m, 1H), 3.73 (dd, *J* = 6.7, 6.0 Hz, 1H), 3.60 (dd, *J* = 9.5, 4.1 Hz, 1H), 3.50 (dd, *J* = 9.5, 5.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 137.3, 135.4, 128.4, 127.8, 127.7, 125.7, 123.7, 117.7, 73.2, 72.3, 57.9, 56.1; FTIR (neat) 3283, 3086, 3030, 2921, 2862, 1641 $cm^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{14}H_{19}NO_3SNa$ 304.0983, found 304.1003.

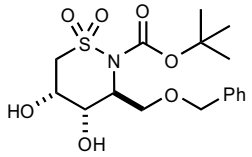
**(*R*)-2H-1,2-thiazine, 3,6-dihydro-3-[(phenylmethoxy)methyl]-1,1-dioxide (2.8)**




In a procedure similar to the preparation of sultam **2.6**, a solution of sulfonamide **2.7** (217 mg, 0.77 mmol) in degassed $CH_2Cl_2$ (154 mL) was treated with Grubbs second generation catalyst (Cat. **C**) (33mg, 0.039 mmol) and the mixture subjected to the RCM reaction. Removal of the residual ruthenium with DMSO, followed by purification via flash chromatography ($SiO_2$, 3:1 Heptane/EtOAc) afforded 180 mg (92%) of sultam **2.8** as an ivory solid.

**Analytical data for 2.8:** TLC $R_f$ = 0.12 (2:1 Heptane/EtOAc); Mp = 79-83 °C; $[\alpha]_D^{25}$ = + 41.7 (*c* = 1.19, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.39-7.29 (m, 5H), 5.86-5.76 (m, 2H), 4.81, (d, *J* = 7.1 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.31-4.26 (m, 1H) 3.74-3.68 (m, 1H), 3.64 (d, *J* = 4.4 Hz, 2H), 3.63-3.58 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 137.1, 128.5, 128.0, 127.8, 127.2, 120.9, 73.3, 70.2, 56.8, 47.5; FTIR (neat) 3252 (N-H), 3032, 2922, 2866, 1653, 1498 $cm^{-1}$; HRMS $(M+NH_4)^+$ calcd for $C_{12}H_{19}N_2O_3S$ 271.1116, found 271.1108.

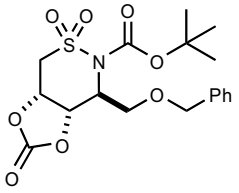
**1,2-thiazine-*N*-carboxylic acid-3,4,5,6-tetrahydro-(3*S*)-[(phenylmethoxy)methyl] -(4*R*,5*S*)-dihydroxy, 1,1-dimethylethyl ester, 1,1-dioxide (2.9)**




To a solution of sultam **2.6** (566 mg, 1.60 mmol), NMO (255 mg, 1.92 mmol) and citric acid (504 mg, 2.40 mmol) in acetone (3 mL) and water (1 mL) was added a 4 % aqueous solution of $OsO_4$ (0.016 mmol, 40 μL) and the reaction stirred at rt for 12 h. The reaction was quenched with a 10% aqueous solution of $Na_2S_2O_3$ (15 mL), extracted with $CH_2Cl_2$ (4 × 15 mL), the organic layers combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography ($SiO_2$, 1:1 Hexanes/EtOAc) afforded 598 mg (96%) of diol **2.9** as a white crystalline solid.

**Analytical data for 2.9:** TLC $R_f$ = 0.11 (1:1 Hexane/EtOAc); Mp = 105-110°C; $[\alpha]_D^{25}$ = + 13.96 (*c* = 1.655, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H), 4.83 (ddd, *J* = 9.2, 6.0, 3.2 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.50 (d, *J* = 12.0 Hz, 1H), 4.33-4.28 (m, 1H), 4.18 (bs, 1H), 3.76 (dd, *J* = 9.6, 9.2 Hz, 1H), 3.66 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.52 (dd, *J* = 12.8, 10.4 Hz, 1H), 3.33 (dd, *J* = 12.8, 4.4 Hz, 1H), 2.65 (s, 2H, O-H), 1.49 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 151.8, 137.4, 128.5, 128.1, 128.0, 85.3, 73.4, 68.5, 66.4, 65.8, 60.5, 52.3, 27.9; FTIR (neat) 3477 (O-H), 3030, 2982, 2932, 2872, 1724 cm$^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{17}H_{25}NO_7SNa$ 410.1250, found 410.1254.

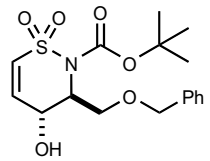
**1,2-thiazine-1,1-dioxide-*N*-carboxylicacid-3,4,5,6-tetrahydro-(3*S*)-[(phenylmethoxy)methyl]-cyclic-(4*R*,5*S*)-cyclocarbonate-1,1-dimethylethyl ester (2.10)**




To a solution of *cis*-diol **2.9** (525 mg, 1.36 mmol) in $CH_2Cl_2$ (38 mL) at -78 °C was added pyridine (3.22 g, 40.8 mmol) and triphosgene (604 mg, 2.03 mmol) in one portion. After stirring for 10 min. at -78 °C the temperature was raised to 0 °C and the reaction stirred at that temperature for 1 h. The crude mixture was quenched with 10 % HCl (15 mL) and extracted with $CH_2Cl_2$ (4 × 25 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford 544 mg (97%) of carbonate **2.10** as a white fluffy solid. The product was used for the next reaction without further purification.

**Analytical data for 2.10:** TLC $R_f$ = 0.35 (1:1 Hexane/EtOAc); Mp = 55-65 °C; $[\alpha]_D^{25}$ = + 6.26 (*c* = 1.405, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 5.17 (ddd, *J* = 8.8, 4.4, 2.0 Hz, 1H), 5.07 (dd, *J* = 8.8, 2.0 Hz, 1H), 4.99 (app q, *J* = 2.8 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.47 (d, *J* = 11.6 Hz, 1H), 4.14 (dd, *J* = 15.6, 4.4 Hz, 1H), 3.86 (dd, *J* = 10.8, 2.8 Hz, 1H), 3.77 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.47 (dd, *J* = 15.2, 2.0 Hz, 1H), 1.55 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 152.2, 151.1, 136.1, 128.9, 128.6, 128.0, 86.2, 74.0, 73.8, 72.4, 70.5, 59.0, 51.6, 27.9; FTIR (neat) 2982, 2939, 1819, 1730, 1454 $cm^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{18}H_{23}NO_8SNa$ 436.1042, found 436.1043.

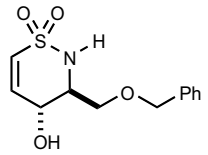
**1, 2thiazine-*N*-carboxylic acid-3, 4-dihydro-(3*S*)-[(phenylmethoxy)methyl]-(4*S*)-hydroxy-1, 1-dimethylethyl ester-1, 1-dioxide (2.11)**




To a solution of carbonate **2.10** (70 mg, 0.174 mmol) in $CH_2Cl_2$ (1.7 mL) was added $Et_3N$ (19.3 mg, 0.19 mmol) and the reaction heated at reflux for 1h. Flash chromatography ($SiO_2$, 2:1 Hexanes/EtOAc) afforded 56.6 mg (91%) of γ-hydroxy sultam **2.11** as a white solid.

**Analytical data for 2.11:** TLC $R_f$ = 0.32 (1:1 Hexanes/EtOAc); Mp = 85-87 °C; $[\alpha]_D^{25}$ = -64.4 (*c* = 1.035, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (m, 5H), 6.47 (ddd, *J* = 10.4, 4.8, 1.2 Hz, 1H), 6.43 (d, *J* = 10.8 Hz, 1H), 4.92-4.87 (m, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 11.6 Hz, 1H), 4.39-4.35 (m, 1H), 3.70 (dd, *J* = 8.8, 4.8 Hz, 2H), 2.47 (d, *J* = 8.5 Hz, 1H), 1.53 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 151.1, 137.3, 133.9, 129.4, 128.4, 127.9, 127.8, 85.7, 73.3, 68.3, 61.4, 61.4, 27.9; FTIR (neat) 3493, 3059, 3035, 2982, 2927, 2872, 1732, 1641 $cm^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{17}H_{23}NO_6SNa$ 392.1144, found 392.1150.

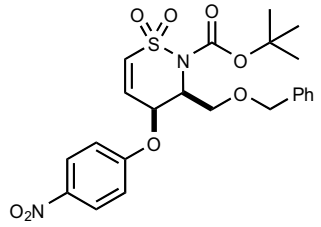
**(3*S*, 4*R*)-2H-1,2thiazine-3, 4-dihydro-3[(phenylmethoxy)methyl]-4-hydroxy-1, 1-dioxide (2.13)**




In a procedure similar to the preparation of sulfonamide **2.7**, γ-hydroxy sultam **2.11** (75.0 mg, 0.20 mmol) in $CH_2Cl_2$ (1.0 mL) was treated with TFA (0.1 mL) and the solution stirred at rt for 30 min. Flash chromatography ($SiO_2$, 1:1 Hexanes/EtOAc) afforded 49.3 mg (92%) of sultam **2.13** as a white crystalline solid.

**Analytical data for 2.13:** TLC $R_f$ = 0.30 (1:1.5 Hezanes/EtOAc); Mp = 115-125 °C; $[\alpha]_D^{25}$ = -15.7 (*c* = 0.255, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.38-7.30 (m, 5H), 6.55 (dd, *J* = 10.8, 2.4 Hz, 1H), 6.37 (dd, *J* = 10.8, 2.0 Hz, 1H), 4.78 (d, *J* = 12.4 Hz, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.55-4.50 (m, 1H), 3.91 (dd, *J* = 9.6, 2.0 Hz, 1H), 3.84-3.77 (m, 1H), 3.61 (dd, *J* = 9.6, 3.6 Hz, 1H), 2.17 (d, *J* = 7.2 Hz, 1H); $^{13}$C NMR (125 MHz, Acetone-$d_6$) δ 141.6, 138.5, 128.8, 128.2, 127.5, 127.4, 72.9, 68.4, 62.8, 59.2; FTIR (neat) 3518, 3240, 3060, 2920, 1623, 1406 $cm^{-1}$; HRMS $(M+NH_4)^+$ calcd for $C_{12}H_{19}N_2O_4$ 287.1066, found 287.1078.

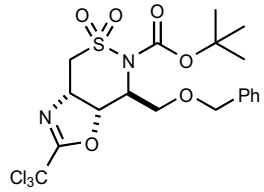
**1,2-thiazine-*N*-carboxylic acid-3, 4-dihydro-(3*S*)-[(phenylmethoxy)methyl]-(4*R*)-(*p*-nitrophenoxy)-1,1-dimethylethyl ester-1, 1-dioxide (2.14)**



To a solution of sultam **2.11** (50 mg, 0.14 mmol) in THF (0.70 mL) was added *p*-nitrophenol (19.0 mg, 0.14 mmol) and $PPh_3$ (40 mg, 0.15 mmol), followed by the dropwise addition of DEAD (26.0 mg, 0.15 mmol, 24 μL) at rt. The reaction was stirred at rt until complete consumption of sultam **2.11** (less than 1 h). Flash chromatography ($SiO_2$, 2:1 Heptane/EtOAc) afforded 30 mg (45 %) of **2.14** as an ivory solid.

**Analytical data for 2.14:** TLC $R_f$ = 0.69 (1:1 Hexanes/EtOAc); Mp = 148-155 °C; $[\alpha]_D^{25}$ = +2.4 (*c* = 0.205, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 9.2 Hz, 2H), 7.33-7.27 (m, 5H), 7.00 (d, *J* = 9.2 Hz, 2H), 6.47 (dd, *J* = 11.2, 2.4 Hz, 1H), 6.40 (ddd, *J* = 11.2, 1.6, 1.6 Hz, 1H), 5.50-5.48 (m, 1H), 5.27-5.21 (m, 1H), 4.55 (d, *J* = 11.2 Hz, 1H), 4.49 (d, *J* = 11.2 Hz, 1H), 4.05 (dd, *J* = 10.0, 10.0 Hz, 1H), 3.89 (dd, *J* = 10.4, 4.4 Hz, 1H), 1.52 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 160.5, 150.8, 142.7, 137.6, 133.6, 129.5, 128.2, 127.8, 127.7, 126.3, 115.2, 85.9, 73.5, 70.0, 65.5, 57.1, 27.8; FTIR (neat) 2980, 2932, 2874, 1732, 1610, 1518, 1342 $cm^{-1}$; HRMS $(M+NH_4)^+$ calcd for $C_{23}H_{30}N_3O_8S$ 508.1754, found 508.1729.

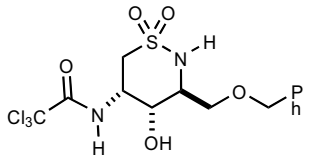
**Trichlorooxazole-containing sultam (2.15)**



To a cold solution (-50 °C) of sultam **2.11** (50 mg, 0.135 mmol) in $CH_2Cl_2$ (1.35 mL) was added $Cl_3CCN$ (20 μL) and DBU (4.1 mg, 0.027 mmol, 4.0 μL). The reaction was stirred until it slowly reached rt. The reaction was quenched with saturated $NH_4Cl$ (15 mL) and extracted with $CH_2Cl_2$ (4 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography ($SiO_2$, 2:1 Hexanes/EtOAc) afforded 66 mg (96 %) of **2.15** a white solid.

**Analytical data for 2.15:** TLC $R_f$ = 0.58 (1:1 Hexanes/EtOAc); Mp = 49-54 °C; $[\alpha]_D^{25}$ = +28.4 (*c* = 0.675, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 5H), 5.27 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.18 (ddd, *J* = 4.4, 4.4, 2.0 Hz, 1H), 4.91 (ddd, *J* = 10.0, 5.6, 2.4 Hz, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.04 (dd, *J* = 14.8, 5.6 Hz, 1H), 3.79 (d, *J* = 4.4 Hz, 2H), 3.53 (dd, *J* = 14.8, 2.4 Hz, 1H), 1.52 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) 163.1, 151.2, 136.5, 128.7, 128.4, 128.0, 85.6, 80.5, 80.5, 73.9, 70.1, 63.6, 58.9, 51.2, 27.9; FTIR (neat) 2982, 2935, 2972, 1728, 1666, 1454, 1369, 1346 cm$^{-1}$; HRMS $(M+H)^+$ calcd for $C_{19}H_{24}Cl_3N_2O_6S$ 513.0421, found 513.0417.

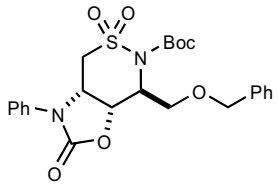
**1,2-thiazine-1,1-dioxide-3,4,5,6-tetrahydrohydro-(3*S*)-[(phenylmethoxy)methyl]-(4*S*)-hydroxy-(5*S*)-(2,2,2-trichloro)acetamide (2.16)**



To a solution of sultam **2.15** (24.0 mg, 0.047 mmol) in $CH_2Cl_2$ (0.5 mL) was added TFA (0.47 mmol, 35 μL) and the reaction stirred at rt for 1 h. Flash chromatography ($SiO_2$, 1:1 Hexanes/EtOAc) afforded 19.4 mg (97%) of trichloroacetimidate **2.16** as a white solid.

**Analytical data for 2.16:** TLC $R_f$ = 0.45 (1:1.5 Hexanes/EtOAc); Mp = 56-64 °C; $[\alpha]_D^{25}$ = -41.5 (*c* = 0.54, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 8.8 Hz, 1H), 7.40-7.30 (m, 5H), 4.99 (d, *J* = 9.6 Hz, 1H), 4.90 (dddd, *J* = 8.0, 4.0, 4.0, 4.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.13 (dd, *J* = 10.4, 4.0 Hz, 1H), 3.92 (dd, *J* = 9.6, 2.4 Hz, 1H), 3.63-3.60 (m, 2H), 3.45 (dd, *J* = 14.0, 4.0 Hz, 1H), 3.37 (dd, *J* = 14.0, 4.0 Hz, 1H), 2.70 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.9, 137.1, 128.6, 128.2, 128.0, 92.0, 73.7, 67.2, 67.1, 55.1, 51.1, 50.3; FTIR (neat) 3470-3447, 3362, 3064, 3032, 2935, 1713, 1630, 1454 $cm^{-1}$; HRMS $(M+H)^+$ calcd for $C_{14}H_{18}Cl_3N_2O_5S$ 431.0002, found 431.0026.

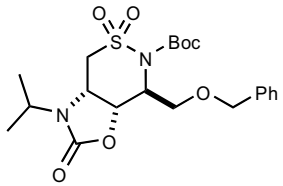
**1,2-thiazine-*N*-carboxylic acid-3,4,5,6-tetrahydro-(3*S*)-[(phenylmethoxy)methyl]-*N*'-phenyl-(4*S*,5*S*)-oxazolidinone-1,1-dimethylethyl ester-1,1-dioxide (2.17)**




To a solution of γ-hydroxy sultam **2.11** (6.0 mg, 0.016 mmol) in DCE (0.16 mL) was added phenyl isocyanate (2.9 mg, 0.024 mmol) and $Et_3N$ (0.16 mg, 0.016 mmol). The reaction was stirred in a pressure tube at reflux (83 °C) until complete by TLC. Flash chromatography ($SiO_2$, 4:1 Hexanes/EtOAc) afforded 5 mg (64%) of bicyclic sultam **2.17** as a white solid.

**Analytical data for 2.17:** TLC $R_f$ = 0.55 (1:1 Hexane/EtOAc); Mp= 160-164 °C; $[\alpha]_D^{25}$ = -52.9 (*c* = 0.17, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45-7.30 (m, 10H), 5.09 (dd, *J* = 9.2, 2.0 Hz, 1H), 5.03-5.01 (m, 1H), 4.93 (ddd, *J* = 9.2, 4.8, 2.0 Hz, 1H), 4.59 (d, J = 11.6 Hz, 1H), 4.53 (d, *J* = 11.6 Hz, 1H), 3.93 (dd, *J* = 14.8, 4.0 Hz, 1H), 3.89 (dd, *J* = 10.4, 3.6 Hz, 1H), 3.83 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.22 (dd, *J* = 15.2, 2.0 Hz, 1H), 1.55 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 153.5, 151.2, 136.5, 134.7, 129.7, 128.9, 128.5, 128.0, 126.7, 123.7, 85.9, 74.1, 71.0, 70.5, 59.6, 55.4, 48.0, 28.0; FTIR (neat) 3063, 2928, 1765, 1724, 1630, 1599, 1456 cm$^{-1}$; HRMS $(M+NH_4)^+$ calcd for $C_{24}H_{32}N_3O_7S$ 506.1961, found 506.1973.

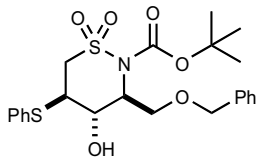
**1,2-thiazine-*N*-carboxylic acid-3,4,5,6-tetrahydro-(3*S*)-[(phenylmethoxy)methyl]-*N*'-isopropyl-(4*S*,5*S*)-oxazolidinone-1,1-dimethylethyl ester-1,1-dioxide (2.18)**




To a solution of γ-hydroxy sultam **2.11**(41.0 mg, 0.11 mmol) in DCM (0.78 mL) was added isopropyl isocyanate (14.0 mg, 0.166 mmol, 16μL) and $Et_3N$ (3.9 mg, 0.039 mmol, 8μL). The reaction was heated at 50 °C in a pressure tube until complete by TLC (~24 h). Flash chromatography ($SiO_2$, 2:1 Hexanes/EtOAc) afforded 39.1 mg (78%) of bicyclic sultam **2.18** as an ivory solid.

**Analytical data for 2.18:** TLC $R_f$ = 0.14 (1:1 Hexanes/EtOAc); Mp = 132-135 °C; $[\alpha]_D^{25}$ =-34.5 (*c* = 0.525, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.40-7.29 (m, 5H), 4.96 (ddd, *J* = 4.0, 4.0, 2.4 Hz, 1H), 4.79 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.33 (ddd, *J* = 8.4, 4.8, 3.2 Hz, 1H), 3.94 (dd, *J* = 15.2, 5.2 Hz, 1H), 3.88-3.85 (m, 1H), 3.85 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.76 (dd, *J* = 10.4, 3.6 Hz, 1H), 3.26 (dd, *J* = 14.8, 3.2 Hz, 1H), 1.54 (s, 9H), 1.34 (d, *J* =7.2 Hz, 3H), 1.32 (d, *J* = 6.8 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 155.1, 151.0, 136.7, 128.8, 128.4, 128.0, 85.7, 73.9, 71.5, 70.3, 59.1, 52.9, 50.6, 46.5, 28.0, 21.5, 20.0; FTIR (neat) 3109, 2980, 1755, 1634, 1520, 1454 $cm^{-1}$; HRMS $(M+NH_4)^+$ calcd for $C_{21}H_{34}N_3O_7S$ 472.2117, found 472.2112.

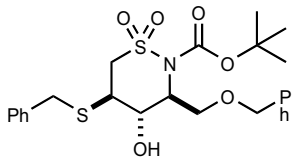
**1,2-thiazine-*N*-carboxylic acid-3,4,5,6-tetrahydro-(3*S*)-[(phenylmethoxy)methyl]-(4*R*)-hydroxy-(5*R*)-phenylthio-1,1-dimethylethyl ester-1,1-dioxide (2.19)**




To a solution of γ-hydroxy sultam **2.11**(32 mg, 0.087 mmol) in $CH_2Cl_2$ (0.87 mL) was added PhSH (10.5 mg, 0.095 mmol, 10 μL) and DMAP (2.0 mg, 0.0174 mmol). The reaction was stirred at rt for 12 h and the solvent removed under reduced pressure. Flash chromatography ($SiO_2$, 4:1 Hexanes/EtOAc) afforded 35 mg (84%, 5.9:1 mixture of inseparable diastereomers) **2.19** as a clear oil.

**Analytical data for 2.19 (major diastereomer):** TLC $R_f$ = 0.59 (1:1 Hexanes/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 6.0, 3.0 Hz, 2H), 7.35-7.28 (m, 6H), 7.22 (dd, *J* = 8.0, 1.5 Hz, 2H), 4.95 (ddd, *J* = 9.0, 6.0, 2.5 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.19 (d, *J* = 2.0 Hz, 1H), 3.87 (ddd, *J* = 13.0, 3.5, 2.0 Hz, 1H), 3.74 (dd, *J* = 10.0, 9.0 Hz, 1H), 3.67 (dd, *J* = 13.5, 12.5 Hz, 1H), 3.64 (dd, *J* = 10.5, 5.5 Hz, 1H), 3.22 (dd, *J* = 13.0, 3.5 Hz, 1H), 2.61 (d, *J* = 3.0 Hz, 1H), 1.50 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 151.5, 137.5, 132.9, 129.7, 128.8, 128.5, 127.9, 127.7, 85.1, 73.3, 68.2, 64.6, 61.7, 50.5, 46.0, 27.9; FTIR (neat) 3504, 3061, 2982, 2932, 1728, 1583, 1454 $cm^{-1}$; HRMS $(M+NH_4)^+$ calcd for $C_{23}H_{33}N_2O_6S_2$ 497.1780, found 497.1778.

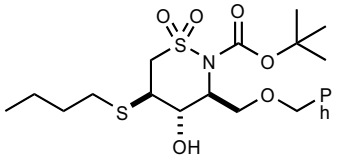
**1,2-thiazine-*N*-carboxylic acid-3,4,5,6-tetrahydro-(3*R*)-[(phenylmethoxy)methyl] -(4*R*)-hydroxy-(5*R*)-benzylthio-1,1-dimethylethyl ester-1,1-dioxide (2.20)**



In a procedure similar to the preparation of sultam **2.19**, a solution of γ-hydroxy sultam **2.11** (29 mg, 0.078 mmol) in $CH_2Cl_2$ (0.78 mL) was treated with $PhCH_2SH$ (10.7 mg, 0.086 mmol, 10 μL) and $Et_3N$ (1.6 mg, 0.0156 mmol, 2.2 μL). The reaction was stirred at rt for 12 h and the solvent removed under reduced pressure. Flash chromatography ($SiO_2$, 3:1 Hexanes/EtOAc) afforded 36.6 mg (major diastereomer) and 1.9 mg (minor diastereomer) of **2.20** (dr ~10:1, 100% combined yield) as clear oils.

**Analytical data for 2.20 (major diastereomer):** TLC $R_f$ = 0.50 (1:1 Hexanes/EtOAc); $[\alpha]_D^{25}$ = + 57.7 (*c* = 0.735, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.36-7.25 (m, 10H), 4.88 (ddd, *J* = 8.0, 6.8, 2.4 Hz, 1H), 4.52 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 12.0 Hz, 1H), 4.00-3.98 (m, 1H), 3.80 (d, *J* = 13.6 Hz, 1H), 3.76 (d, *J* = 13.6 Hz, 1H), 3.58 (dd, *J* = 8.0, 1.2 Hz, 1H), 3.57 (d, *J* = 13.2 Hz, 1H), 3.54 (d, *J* = 13.2 Hz, 1H) , 3.39 (ddd, *J* = 13.2, 3.2, 2.0 Hz, 1H), 3.01 (dd, *J* = 13.2, 3.2 Hz, 1H), 2.57 (s, 1H), 1.48 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 150.4, 136.6, 135.7, 127.9, 127.8, 127.4, 126.9, 126.8, 126.7, 83.9, 72.1, 67.3, 63.7, 60.4, 49.5, 40.7, 34.8, 26.9; FTIR (neat) 3504, 2980, 2930, 1726, 1602, 1454, 1138 $cm^{-1}$; HRMS $(M+NH_4)^+$ calcd for $C_{24}H_{35}N_2O_6S_2$ 511.1937, found 511.1939.

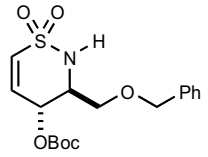
**1,2-thiazine-*N*-carboxylic acid-3,4,5,6-tetrahydro-(3*S*)-[(phenylmethoxy)methyl]-(4*R*)-hydroxy-(5*R*)-butylthio-1,1-dimethylethyl ester-1,1-dioxide (2.21):**



In a procedure similar to the preparation of sultam **2.19**, a solution of γ-hydroxy sultam **2.11** (27 mg, 0.073 mmol) in $CH_2Cl_2$ (0.73 mL) was treated with BuSH (7.2mg, 0.080 mmol, 10 μL) and $Et_3N$ (2.2 mg, 0.0219 mmol, 3.0 μL). The reaction was stirred at rt for 12 h and the solvent removed under reduced pressure. Flash chromatography ($SiO_2$, 3:1 Hexanes/EtOAc) afforded 29.6 mg (88%) of **2.21** as an inseparable mixture of diastereomers (dr ~4.5:1) as a clear oil.

**Analytical data for 2.21 (major diastereomer):** TLC $R_f$ = 0.50 (1:1 Hexanes/EtOAc); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 5H), 4.97 (ddd, *J* = 9.0, 5.5, 2.5 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.12 (app q, *J* = 2.0 Hz, 1H), 3.80 (dd, *J* = 9.5, 9.5 Hz, 1H), 3.67 (dd, *J* = 10.0, 6.0 Hz, 1H), 3.56 (dd, *J* = 13.0, 13.0 Hz, 1H), 3.46 (ddd, *J* = 13.0, 3.0, 2.0 Hz, 1H), 3.17 (dd, *J* = 13.0, 3.0 Hz, 1H), 2.61 (d, *J* = 2.5 Hz, 1H), 2.57 (ddd, *J* = 7.5, 7.5, 2.0 Hz, 2H), 1.57-1.54 (m, 2H), 1.50 (s, 9H), 1.42-1.37 (m, 2H), 0.92 (t, *J* = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 151.4, 137.6, 128.5, 127.9, 127.8, 85.0, 73.2, 68.2, 64.6, 61.3, 50.7, 42.6, 31.6, 31.3, 27.9, 21.9, 13.6; FTIR (neat) 2959, 2932, 1728, 1624, 1607, 1497, 1454 cm$^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{21}H_{33}NO_6S_2Na$ 482.1647, found 482.1638.

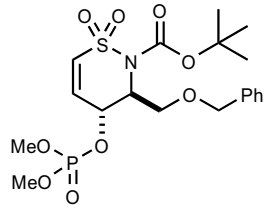
**1,2-thiazine-1,1-dioxide-3,4,-dihydro-(3S)-[(phenylmethoxy)methyl]-(4*S*)-tert-butylcarbonate (2.22)**




To a solution of sultam **2.11** (25 mg, 0.067 mmol) in THF (0.67 mL) was added $Cs_2CO_3$ (24 mg, 0.074 mmol) and the reaction stirred at 60 °C for 1 h. The crude product was filtered and purified by flash chromatography ($SiO_2$, 4:1 Hexanes/ EtOAc) to afford 17.9 mg (72%) of sultam **2.22** as a clear oil.

**Analytical data for 2.22:** TLC $R_f$ = 0.64 (2:1 Hexanes/EtOAc); $[\alpha]_D^{25}$ = -75.9 (*c* = 0.20, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H), 6.63 (dd, *J* = 11.2, 2.0 Hz, 1H), 6.36 (dd, *J* = 11.2, 2.0 Hz, 1H), 5.48 (ddd, *J* = 12.0, 4.0, 2.0 Hz, 1H), 4.98 (d, *J* = 12.4 Hz, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.00 (dddd, *J* = 12.5, 5.0, 2.5, 2.5 Hz, 1H), 3.68 (dd, *J* = 10.0, 1.6 Hz, 1H), 3.59 (dd, *J* = 10.0, 2.8 Hz, 1H), 1.50 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 153.3, 137.0, 136.3, 130.3, 128.6, 128.2, 128.0, 83.9, 73.7, 66.7, 66.0, 56.0, 27.7; FTIR (neat) 3285, 3063, 2982, 1743, 1618, 1456, 1369, 1151 $cm^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{17}H_{23}NO_6SNa$ 392.1144, found 392.1138.

**1,2-thiazine-1,1-dioxide-*N*-carboxylic acid-3, 4-dihydro-(3*S*)-[(phenylmethoxy)-methyl]-1,1-dimethylethyl ester-(4*S*)-dimethylphosphate (2.23)**

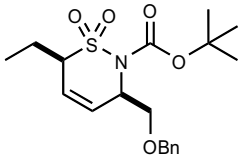


To a solution of γ-hydroxy sultam **2.11** (144 mg, 0.39 mmol) in $CH_2Cl_2$ (4 mL) at 0 °C was added *N*-methylimidazole (96 mg, 1.17 mmol, 84 μL) and $(MeO)_2P(O)Cl$ (112.6 mg, 0.78 mmol, 84 μL). The ice bath was removed and the reaction stirred at rt for 1 h. The reaction was quenched with a saturated solution of $NH_4Cl$ (15 mL) and extracted with $CH_2Cl_2$ (4 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography ($SiO_2$, 1:2 hexanes/EtOAc) afforded 159 mg (85%) of sultam **2.23** as a clear oil.

**Analytical data for 2.23:** TLC $R_f$ = 0.37 (1:2.5 Heptane/EtOAc); $[\alpha]_D^{25}$ = -83.9 (*c* = 1.355, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.31-7.23 (m, 5H), 6.46 (d, *J* = 10.6 Hz, 1H), 6.43 (ddd, *J* = 10.6, 5.3, 1.5 Hz, 1H), 5.06-5.02 (m, 1H), 4.93 (ddd, *J* = 7.7, 5.4, 2.0 Hz, 1H), 4.51 (d, *J* = 11.8 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 3.72 (d, $J_{HP}$ =11.3 Hz, 3H), 3.69 (d, $J_{HP}$ = 11.3 Hz, 3H), 3.62 (dd, *J* = 8.4, 1.3 Hz, 2H), 1.46 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 150.6, 137.2, 131.6, 129.7 (d, $J_{CP}$ = 15.0 Hz), 128.5, 128.0, 127.8, 85.8, 73.4, 67.5, 65.2 (d, $J_{CP}$ = 20.0 Hz), 59.4 (d, $J_{CP}$ = 20.0 Hz), 54.8 (d, $J_{CP}$ = 25.0 Hz), 54.8 (d, $J_{CP}$ = 20.0 Hz), 27.9; $^{31}$P NMR (400 MHz, $CDCl_3$) δ

1.77; FTIR (neat) 3833, 2981, 2959, 1736, 1647, 1456 $cm^{-1}$; HRMS $(M+NH_4)^+$ calcd for $C_{19}H_{32}N_2O_9PS$ 495.1566, found 495.1560.

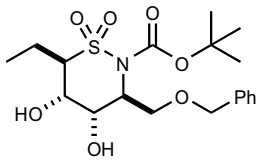
**1,2-thiazine-*N*-carboxylic acid-3,6-dihydro-(3*R*)-[(phenylmethoxy)methyl]-(6*R*)-ethyl- 1,1-dimethylethyl ester-1,1-dioxide (2.24)**




To a solution of CuCN·2LiCl (1 M, 0.56 mmol) at -78° C was added $Et_2Zn$ (1 M, 0.56 mmol) and the mixture stirred at that temperature for 1.5 h. A solution of phosphate **2.23** (26.5 mg, 0.056 mmol) in THF (0.56 mL) was added to the ethyl cuprate mixture and the solution stirred until it warmed up to -20 °C. The reaction was quenched with a saturated solution of $NH_4Cl$ (10 mL) and extracted with $CH_2Cl_2$ (4 × 10 mL), the organic layers combined, dried over $MgSO_4$, filtered and concentrated. Flash chromatography ($SiO_2$, 7:1 Hexanes/EtOAc) afforded 15.5 mg (74%) of sultam **2.24** as a white solid.

**Analytical data for 2.24:** TLC $R_f$ = 0.69 (2:1 Hexanes/EtOAc); Mp = 60-65 °C; $[\alpha]_D^{25}$ = + 85.7 (*c* = 0.68, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.34-7.27 (m, 5H), 5.93 (ddd, *J* = 10.8, 3.2, 3.2 Hz, 1H), 5.60 (ddd, *J* = 10.8, 2.0, 1.6 Hz, 1H), 5.28-5.22 (m, 1H), 4.48 (s, 2H), 3.74-3.67 (m, 3H), 2.11-2.05 (m, 1H), 1.69-1.60 (m, 1H), 1.42 (s, 9H), 1.07 (t, 7.4 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 150.7, 137.9, 128.1, 127.6, 127.6, 125.8, 122.7, 84.4, 73.1, 70.9, 60.5, 59.9, 27.9, 21.7, 10.9; FTIR (neat) 2978, 2935, 1716, 1616, 1456, 1169 $cm^{-1}$; HRMS $(M+NH_4)^+$ calcd for $C_{19}H_{31}N_2O_5S$ 399.1954, found 399.1953.

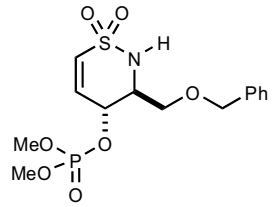
**1,2-thiazine-*N*-carboxylic acid-3,4,5,6-tetrahydro-(3*R*)-[(phenylmethoxy)methyl] -(4*R*,5*S*)-dihydroxy-(6*R*)-ethyl- 1,1-dimethylethyl ester-1,1-dioxide (2.25)**




To a stirring solution of **s**ultam **2.24** (10.8 mg, 0.028 mmol) in acetone (1.5 mL) and water (0.5 mL) was added citric acid (9.0 mg, 0.042 mmol), NMO (6.0 mg, 0.033 mmol) and 1 drop of $OsO_4$ (4 % solution in water). The reaction was stirred at rt for 12 h, then quenched with a 10% aqueous solution of $Na_2SO_3$ and extracted with $CH_2Cl_2$ (4 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography ($SiO_2$, 1:1 Hexanes/EtOAc) afforded 9.1 mg (78%) of diol **2.25** as an ivory solid.

**Analytical data for 2.25:** TLC $R_f$ = 0.16 (1:1 Hexanes/EtOAc); Mp = 100-105 °C; $[\alpha]_D^{25}$ = + 50.8 (*c* = 0.13, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.37-7.30 (m, 5H), 4.72 (ddd, *J* = 9.6, 5.6, 4.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 11.6 Hz, 1H), 4.27 (bs, 1H), 3.98 (dd, *J* = 6.8, 6.0 Hz, 1H), 3.82 (dd, *J* = 9.6, 9.2 Hz, 1H), 3.72 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.38 (ddd, *J* = 8.0, 6.0, 6.0 Hz, 1H), 2.74 (bs, 1H), 2.51 (d, *J* = 7.6 Hz, 1H), 2.04 (ddd, *J* = 13.6, 7.6, 7.6 Hz, 1H), 1.50 (s, 9H), 1.20 (t, *J* = 7.6 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 151.9, 137.4, 128.5, 128.0, 127.9, 84.9, 73.5, 70.3, 69.7, 68.0, 63.9, 59.8, 27.9, 18.8, 11.9; FTIR (neat) 3479, 2979, 2933, 2879, 1722, 1367, 1055 cm$^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{19}H_{29}NO_7SNa$ 438.1563, found 438.1551.

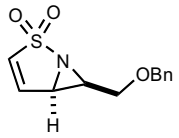
**1,2-thiazine-1,1-dioxide-3,4-dihydro-(3*S*)-[(phenylmethoxy)methyl]-(4*R*)-dimethylphosphate (2.26)**



To a stirring solution of **s**ultam **2.23** (12.0 mg, 0.25 mmol) in $CH_2Cl_2$ (0.25 mL) was added $FeCl_3$ (4.0 mg, 0.025 mL) in one portion and the reaction stirred at rt for 30 min. The crude mixture was quenched with water (10 mL) and extracted with $CH_2Cl_2$ (4 × 15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography ($SiO_2$, 1:2 Hexane/EtOAc) afforded 5.6 mg (60%) of sultam **2.26** as a white solid.

**Analytical data for 2.26:** TLC $R_f$ = 0.14 (1:2 Hexanes/EtOAc); Mp = 80-84° C; $[\alpha]_D^{25}$ = -49.6 (*c* = 1.11, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.37-7.32 (m, 5H), 6.64 (dd, *J* = 10.8, 2.0 Hz, 1H), 6.52 (dd, *J* = 10.8, 2.0 Hz, 1H), 5.18 (dddd, *J* = 9.2, 9.2, 2.0, 2.0 Hz, 1H), 5.00 (d, *J* = 12.0 Hz, 1H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.00-3.95 (m, 1H), 3.87 (dd, *J* = 9.6, 2.0 Hz, 1H), 3.79 (d, $J_{HP}$= 11.2 Hz, 3H), 3.75 (d, $J_{HP}$ = 11.2 Hz, 3H), 3.65 (dd, *J* = 9.6, 2.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 137.1, 136.7, 130.4, 128.6, 128.2, 128.0, 73.7, 67.2 (d, $J_{CP}$ = 20.0 Hz), 66.9, 57.1 (d, $J_{CP}$ = 35.0 Hz), 54.9 (d, $J_{CP}$ = 30.0 Hz), 54.8 (d, $J_{CP}$ = 30.0 Hz); $^{31}$P NMR (400 MHz, $CDCl_3$) δ 1.60; FTIR (neat) 3232, 3119, 2957, 1610, 1454, 1155, 1092 $cm^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{14}H_{20}NO_7PSNa$ 400.0596, found 400.0578.

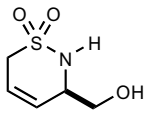
**Aziridine-Containing Sultam(2.29)**




To a solution of sultam **2.26** (21.7 mg, 0.0575 mmol) in THF (0.58 mL) was added $Cs_2CO_3$ (56 mg, 0.173 mmol) and the reaction stirred at 60 °C for 1 h. The product was filtered and purified by flash chromatography ($SiO_2$, 1:1 Hexanes/EtOAc) to afford 15 mg (100%) of aziridine **2.29** as a light-yellow oil.

**Analytical data for 2.29:** TLC $R_f$ = 0.43 (1:2 Hexanes/EtOAc); $[\alpha]_D^{25}$ = -38.6 (*c* = 0.35, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.38-7.31 (m, 5H), 6.96 (ddd, *J* = 6.0, 1.0, 1.0 Hz, 1H), 6.40 (d, *J* = 6.0 Hz, 1H), 4.60 (d, *J* = 12.4 Hz, 1H), 4.56 (d, *J* = 12.8 Hz, 1H), 3.80 (dd, *J* = 11.6, 4.4 Hz, 1H), 3.68 (m, 1H), 3.58 (dd, *J* = 11.2, 4.8 Hz, 1H), 2.78 (q, *J* = 4.0 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 136.8, 136,2, 127.6, 127.0, 126.9, 125.0, 72.6, 66.8, 55.5, 46.2; FTIR (neat) 3080, 2920, 1609 $cm^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{12}H_{13}NO_3SNa$ 274.0514, found 274.0515.

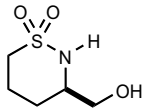
**(*R*)-(1,1-dioxo-3,6-dihydro-[1,2]thiazin-3-yl)-methanol (2.30)**



To a solution of sultam **2.8** (56 mg, 0.158 mmol) in $CHCl_3$ (1.6 mL) was added TMSI (95 mg, 0.475 mmol, 65 μL) and the reaction heated at 70 °C for 7 h. The reaction was quenched with MeOH (4 mL) and the solvent removed under reduced pressure. Flash chromatography ($SiO_2$, 1:1 Hexanes/EtOAc) afforded 12 mg (47%) of sultam **2.30** as a clear oil.

**Analytical data for 2.30:** TLC $R_f$ = 0.14 (1: 3 Hexane/EtOAc); $[\alpha]_D^{25}$ = +63.1 (*c* = 0.555, EtOH); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.93-5.88 (m, 1H), 5.81 (dd, *J* = 10.8, 2.0 Hz, 1H), 4.96 (d, *J* = 6.4 Hz, 1H, N-H), 4.27-4.22 (m, 1H), 3.90-3.83 (m, 2H), 3.74-3.68 (m, 2H), 2.37 (t, *J* = 5.6 Hz, O-H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 126.6, 121.7, 63.4, 58.8, 47.7; FTIR (neat) 3475, 3254, 2960, 1150 $cm^{-1}$; HRMS $(M+Na)^+$ calcd for $C_5H_9NO_3SNa$ 186.0201, found 186.0212.

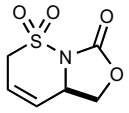
**(*R*)-(1,1-dioxo-[1,2]thiazinan-3-yl)-methanol (2.31)**



A solution of 10 % Pd/C (122 mg) in 95 % EtOH (10 mL) was stirred for 15 min. followed by the addition of sultam **2.8** (244 mg, 0.96 mmol). The air was removed by suction, a $H_2$ ballon was inserted and the reaction stirred at rt for 7 h. the product was filtered through celite and purified by flash chromatography ($SiO_2$, 1:1 hexane/ EtOAc, then 100% EtOAc) to afford 126 mg (79%) of **2.31** as white crystals.

**Analytical data for 2.31:** TLC $R_f$ = 0.26 (100% EtOAc); $[\alpha]_D^{25}$ = -14.4 (*c* = 0.20, MeOH); Mp = 110-115 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 4.50 (d, *J* = 6.4 Hz, 1H, N-H), 3.80 (dd, *J* = 10.8, 3.6 Hz, 1H), 3.66 (dd, *J* =10.8, 4.4 Hz, 1H), 3.63-3.56 (m, 1H), 3.20 (ddd, *J* = 13.6, 3.6, 3.6 Hz, 1H), 2.89 (ddd, *J* = 13.2, 9.6, 7.2 Hz, 1H), 2.26 (m, 2H), 1.71 (ddd, *J* = 14.0, 6.4, 3.2 Hz, 1H), 1.63 (bs, 1H), 1.59-1.50 (m, 1H); $^{13}$C NMR (125 MHz, MeOD) δ 63.0, 57.4, 47.7, 25.0, 21.8; FTIR (neat) 3431, 3250, 2935, 1151 $cm^{-1}$; HRMS $(M+H)^+$ calcd for $C_5H_{12}NO_3S$ 166.0538, found 166.0540.

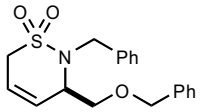
**(*R*)-2H,7H-Oxazolo[3,4β][1,2]thiazin-7-one-4α,5-dihydro-1-dioxide (2.32)**



To a solution of **s**ultam **2.30** (30 mg, 0.18 mmol) in $CH_2Cl_2$ (18 mL) at -50 °C was added pyridine (43 mg, 0.54 mmol, 44 μL) and triphosgene (65 mg, 0.22 mmol) portionwise. The reaction was stirred until it reached rt. The reaction was quenched with $NH_4Cl$ (15 mL) and extracted with $CH_2Cl_2$ (4 × 15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography ($SiO_2$, 1:1 Hexanes/EtOAc) afforded 18 mg (53 %) of carbamate **2.32** as a clear oil.

**Analytical data for 2.32** TLC $R_f$ = 0.27 (1: 2 Hexane/EtOAc); $[\alpha]_D^{25}$ = +17.9 (*c* = 1.1, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.95 (dddd, *J* = 10.4, 4.0, 4.0, 2.0 Hz, 1H), 5.89 (dddd, *J* = 10.4, 2.4, 1.2, 1.2 Hz, 1H), 5.12-5.10 (m, 1H), 4.53 (dd, *J* = 8.4, 8.4 Hz, 1H), 4.25 (dd, *J* = 8.8, 2.8 Hz, 1H), 4.09 (dddd, *J* = 17.2, 3.2, 2.4, 2.4 Hz, 1H), 3.80 (dddd, *J* = 17.2, 6.0, 2.8, 1.2 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 151.2, 126.3, 122.2, 66.6, 59.7, 48.0; FTIR (neat) 2962, 1743; HRMS $(M+Na)^+$ calcd for $C_6H_7NO_4SNa$ 211.9994, found 212.0008.

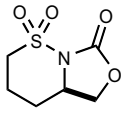
**1,2-thiazine-*N*-benzyl-3,6-dihydro-3-[(phenylmethoxy)methyl]-1,1-dioxide (2.33)**




To a stirring solution of sultam **2.8** (262 mg, 1.03 mmol) in THF (10.3 mL) was added $Cs_2CO_3$ (1.0 g, 3.09 mmol) and BnBr (265 mg, 1.55 mmol, 0.18 mL) and the reaction stirred at 80 °C for 1 h. The product was filtered and the solvent removed under reduced pressure. Flash chromatography ($SiO_2$, 3:1 Hexane/EtOAc) afforded 305 mg (86%) of benzyl sultam **2.33** as a light-yellow oil.

**Analytical data for 2.33:** TLC $R_f$ = 0.34 (2:1 Hexane/EtOAc); [α] = + 92.3 (*c* = 1.45, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.35-7.28 (m, 8H), 7.24-7.22 (m, 2H), 5.90 (dddd, *J* = 10.4, 3.6, 2.0, 2.0 Hz, 1H), 5.79-5.74 (m, 1H), 4.52 (d, *J* = 14.4 Hz, 1H), 4.44 (d, J = 12.4 Hz, 1H), 4.42 (d, *J* = 14.4 Hz, 1H), 4.41 (d, *J* = 12.4 Hz, 1H), 4.15-4.09 (m, 1H), 3.78 (dd, *J* = 9.6, 6.4 Hz, 1H), 3.74 (dd, *J* = 9.6, 7.2 Hz, 1H), 3.64-3.62 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 137.8, 135.9, 128.6, 128.4, 128.3, 127.9, 127.6, 127.5, 126.4, 119.3, 73.2, 71.5, 61.2, 53.0, 46.4; IR (neat) 3165, 3061, 2916, 1606 cm$^{-1}$; HRMS $(M+H)^+$ calcd for $C_{19}H_{22}NO_3S$ 344.1320, found 344.1331.

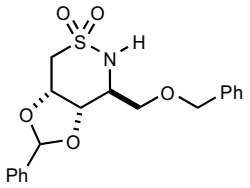
**(*R*)-2H,7H-Oxazolo[3,4β][1,2]thiazinan-7-one-4α,5-dihydro-1-dioxide (2.34)**



In a procedure similar to the preparation of carbamate **2.32**, a solution of sultam **2.31** (12.5 mg, 0.076 mmol) in $CH_2Cl_2$ (1.89 mL) was treated with trtriphosgene (34 mg, 0.114 mmol) and pyridine (18 mg, 0.228 mmol, 18 μL) to afford 7 mg of carbamate **2.34** (48%) as a white crystalline solid.

**Analytical data for 2.34**: TLC $R_f$ = 0.23 (1:2 Hexanes/EtOAc); Mp = 165-170 °C; $[\alpha]_D^{25}$ = - 7.2 (*c* = 0.49, $CH_3C(O)CH_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 4.50-4.44 (m, 2H), 4.04-4.00 (m,1H), 3.32 (ddd, *J* = 13.5, 3.5, 3.5 Hz, 1H), 3.21 (ddd, *J* = 13.0, 13.0, 4.5 Hz, 1H), 2.40-2.36 (m, 1H), 2.35-2.30 (m, 1H), 2.00 (dddd, *J* = 14.5, 4.0, 4.0, 3.0 Hz, 1H), 1.73-1.64 (m, 1H)**;** $^{13}$C NMR (125 MHz, $CDCl_3$) δ 150.2, 67.2, 58.3, 50.8, 28.0, 22.9; IR (neat) 2980, 2924, 1774, 1381, 1362, 1190, 1151 $cm^{-1}$; HRMS $(M+Na)^+$ calcd for $C_6H_9NO_4SNa$ 214.0150, found 214.0140.

**1,2-thiazine-3,4,5,6-tetrahydro-(3*S*)-[(phenylmethoxy)methyl]-(4*R*,5*S*)-phenyldioxole-1,1-dioxide (2.35)**

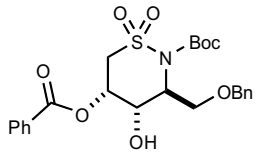


To a solution of diol **2.9** (118 mg, 0.30 mmol), *p*-TsOH (11.0 mg, 0.06 mmol) and benzaldehyde (38 mg, 0.036 mmol) in dry benzene (3 mL) was added 4 Å molecular sieves. The reaction was stirred at 80 °C in a pressure tube for 12 h. The reaction was quenched with a saturated aqueous solution of sodium bisulfite (15 mL) and extracted with $CH_2Cl_2$ (4 × 10 mL). The organic layers were combined, dried over MgSO4, filtered and concentrated under reduced pressure. Flash chromatography ($SiO_2$, 2:1 Hexanes/EtOAc) afforded 30.6 mg (major diastereomer) and 22.0 mg (minor diastereomer) (66% combined yield; dr = 1.4:1) of **2.35** as white solids.

**Analytical data for 2.35 (major diastereomer):** TLC $R_f$ = 0.41 (1:1 Hexanes/EtOAc); Mp = 100-105 °C; $[\alpha]_D^{25}$ = -40.3 (*c* = 1.66, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.59-7.50 (m, 2H), 7.41-7.39 (m, 3H), 7.36-7.28 (m, 5H), 5.95 (s, 1H), 4.76 (d, *J* = 10.0 Hz, 1H), 4.72 (q, *J* = 5.2 Hz, 1H), 4.52 (s, 2H), 4.39 (dd, *J* = 8.8, 5.6 Hz, 1H), 3.81-3.77 (m,1H), 3.76-3.72 (m, 2H), 3.65 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.51 (dd, *J* = 15.2, 5.2 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 137.1, 136.5, 129.8, 128.7, 128.6, 128.2, 128.0, 126.5, 104.8, 75.0, 73.7, 69.4, 68.2, 55.7, 49.5; FTIR (neat) 3247, 3029, 2929, 1637, 1454 cm$^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{19}H_{21}NO_5SNa$ 398.1038, found 398.1031.

**Analytical data for minor diastereomer:** TLC $R_f$ = 0.43 (1:1 Hexanes/EtOAc); Mp = 112-118 °C; $[\alpha]_D^{25}$ = -65.0 (*c* = 1.335, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.45-7.32 (10 H), 6.29 (s, 1H), 4.80 (d, *J* = 10.0 Hz, 1H), 4.68 (ddd, *J* = 4.8, 4.8, 3.2 Hz, 1H), 4.57 (s, 2H), 4.51 (dd, *J* = 8.8, 5.2 Hz, 1H), 3.94 (ddd, *J* = 9.2, 3.2, 3.2 Hz, 1H), 3.89 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.76 (dd, *J* = 9.6, 3.2 Hz, 1H), 3.72 (dd, *J* = 15.2, 3.2 Hz, 1H), 3.40 (dd, *J* = 15.2, 4.8 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 137.0, 136.0, 128.3, 127.6, 127.5, 127.2, 127.0, 124.9, 102.4, 72.7, 72.1, 68.9, 67.2, 53.0, 48.2; FTIR (neat) 3451, 3031, 2929, 1637, 1459 $cm^{-1}$; HRMS $(M+H)^+$ calcd for $C_{19}H_{22}NO_5S$ 376.1219, found 376.1221.

**1,2-thiazine-*N*-carboxylic acid-3,4,5,6-tetrahydro-(3*S*)-[(phenylmethoxy)methyl]-(4*R*)-hydroxy-(5*S*)-*O*-benzoyl, 1,1-dimethylethyl ester, 1,1-dioxide (2.36)**

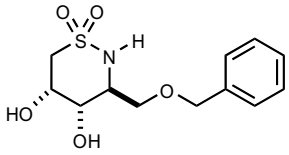



To a stirring cold (0 °C) solution of diol **2.9** (100 mg, 0.258 mmol) DMAP (3.0 mg, 0.0258 mmol) and $Et_3N$ (27.4 mg, 0.270 mmol, 38 μL) in $CH_2Cl_2$ (25 mL) was slowly added a solution of benzoyl chloride (27.4 mg, 0.270 mmol, 38 μL) in $CH_2Cl_2$ (1 mL). The reaction was stirred at 0 °C for 2 h. The product was quenched with an aqueous solution of $NaHCO_3$ (15 mL) and extracted with $CH_2Cl_2$ (4 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography ($SiO_2$, 3:1 Hexanes/EtOAc) afforded 64 mg (50 %) of benzoylated sultam **2.36** as a white solid.

**Analytical data for 2.36:** TLC $R_f$ = 0.56 (1:1 Hexanes/EtOAc); Mp =120-125 °C; $[\alpha]_D^{25}$ = -47.6 (*c* = 0.45, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.4 Hz, 2H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 4.4 Hz, 2H), 7.32-7.28 (m, 3H), 5.63 (ddd, *J* = 10.4, 4.0, 2.0 Hz, 1H), 4.94 (ddd, *J* = 9.2, 6.4, 3.6 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.50 (t, *J* = 2.4 Hz, 1H), 3.88 (dd, *J* = 10.8, 10.0 Hz, 1H), 3.84 (dd, *J* = 12.8, 10.8 Hz, 1H), 3.78 (dd, *J* = 10.0, 6.4 Hz, 1H), 3.54 (dd, *J* = 12.8, 4.4 Hz, 1H), 2.53 (s, 1H, O-H), 1.49 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 165.0, 151.4, 137.5, 133.9, 129.9, 128.8, 128.7, 128.5, 127.9, 127.9, 85.2, 73.5, 68.6, 68.4, 65.3, 60.4, 50.4, 27.9; FTIR (neat) 3512, 2979,

2955, 1726, 1600, 1452 $cm^{-1}$; HRMS $(M+NH_4)^+$ calcd for $C_{24}H_{33}N_2O_8S$ 509.1958, found 509.1948.

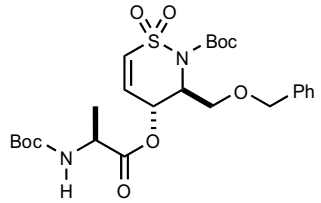
**1,2-thiazine-3,4,5,6-tetrahydro-3-[(phenylmethoxy)methyl]-4,5-dihydroxy-1,1-dioxide (2.37)**




To a solution of diol **2.9** (171 mg, 0.44 mmol) in $CH_2Cl_2$ (1.0 mL) was added TFA (0.2 mL) dropwise. The reaction was stirred at rt for 1 h at rt. Upon completion, the reaction was quenched with saturated $NaHCO_3$ (15 mL), extracted with $CH_2Cl_2$ (4 × 15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography ($SiO_2$, 1:3 Hexanes/ EtOAc) afforded 112 mg (88%) of the diol sultam **2.37** as a white crystalline solid.

**Analytical data for 2.37:** TLC $R_f$ = 0.22 (1:1 Hexanes/EtOAc); Mp = 115-117°C; $[\alpha]_D^{25}$ = -35.6 (*c* = 0.93, MeOH); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.39-7.31 (m, 5H), 5.01 (d, *J* = 8.8 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.34-4.30 (m, 1H), 3.90 (dd, *J* = 9.6, 3.2 Hz, 1H), 3.74 (ddd, *J* = 10.0, 10.0, 3.2 Hz, 1H), 3.63 (dd, *J* = 12.0, 3.6 Hz, 1H), 3.61 (d, *J* = 9.2 Hz, 2H), 3.44 (dd, *J* = 14.4, 4.0 Hz, 1H), 3.27 (dd, *J* = 14.4, 3.2 Hz, 1H), 2.61 (d, *J* = 9.6 Hz,1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 137.2, 128.6, 128.2, 128.0, 73.7, 68.3, 67.5, 66.6, 55.0, 53.3; FTIR (neat) 3460, 3444, 3256, 2930, 2872, 1607, 1497, 1454, 1155 $cm^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{12}H_{17}NO_5SNa$ 310.0725, found 310.0738.

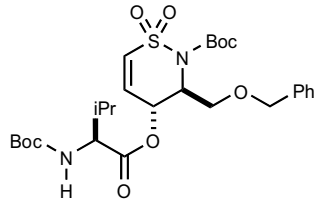
**OACC Coupled Alanine Sultam(2.38)**




To a solution of sultam **2.11** (12.0 mg, 0.032 mmol), DMAP (1.0 mg, 0.0096 mmol) and Boc-(L)-Alanine (7.4 mg, 0.039 mmol) in $CH_2Cl_2$ (0.1 mL) was added a solution of OACC (20.0 mg, 0.051 mmol) in $CH_2Cl_2$ (0.22 mL). The reaction was stirred at rt for 12 h after which MP-carbonate resin (8 mg) was added and the reaction stirred for another 2 h. The solvent was removed under reduced pressure, the crude mixture mixed with silica, followed by filtration via silica plug ($SiO_2$, 100% EtOAc) to afford 15.9 mg (92%) of **2.38** as a clear oil.

**Analytical data for 2.38:** TLC $R_f$ = 0.10 (2:1 hexanes/EtOAc); $[\alpha]_D^{25}$ = -105.7 (*c* = 0.48, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.36-7.29 (m, 5H), 6.51 (d, *J* = 10.8 Hz, 1H), 6.45 (ddd, *J* = 10.8, 5.6, 1.6 Hz, 1H), 5.38 (dd, *J* = 5.6, 2.0 Hz, 1H), 4.99 (dddd, *J* = 7.6, 7.6, 1.6, 1.6 Hz, 1H), 4.92 (m, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.34 (m, 1H), 3.71 (d, *J* = 7.6 Hz, 2H), 1.54 (s, 9H), 1.44 (9H), 1.37 (d, *J* = 7.2 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 172.3, 155.1, 150.6, 137.2, 132.1, 129.3, 128.5, 128.3, 128.2, 85.8, 80.1, 73.4, 67.5, 62.9, 58.2, 49.3, 28.3, 28.0, 18.3; FTIR (neat) 3393, 2980, 1736, 1717, 1618, 1369, 1338, 1163; HRMS $(M+Na)^+$ calcd for $C_{25}H_{36}N_2O_9SNa$ 563.2039, found 563.2014.

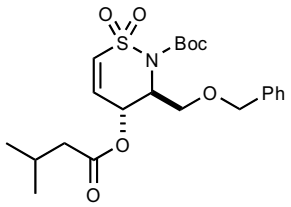
**OACC Coupled Valine Sultam (2.39)**




In a procedure similar to the preparation of sultam **2.38**, sultam **2.11** (27 mg, 0.073 mmol), DMAP (3 mg, 0.219 mmol) and Boc-(L)-Valine (24 mg, 0.109 mmol) in $CH_2Cl_2$ (0.15 mL) were utilized in the coupling reaction with OACC (46 mg, 0.146 mmol) in $CH_2Cl_2$ (0.55 mL). Filtration via silica plug ($SiO_2$, 1:1 Hexanes/EtOAc) afforded 44 mg (100%) of **2.39** as a clear oil.

**Analytical data for 2.39**: TLC $R_f$ = 0.64 (1:1 hexanes/EtOAc); $[\alpha]_D^{25}$ = -28.8 (*c* = 0.48, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.35-7.30 (m, 5H), 6.50 (d, *J* = 10.4 Hz, 1H), 6.47 (ddd, *J* = 10.4, 6.4, 1.2 Hz, 1H), 5.37 (dd, *J* = 4.8, 1.6 Hz, 1H), 5.03-4.99 (m, 1H), 4.93 (d, *J* = 8.8 Hz, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 4.27 (dd, *J* = 8.0, 4.4 Hz, 1H), 3.70 (d, *J* = 7.6 Hz, 2H), 2.17-2.12 (m, 1H), 1.53 (s, 9H), 1.45 (s, 9H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.3, 155.6, 150.5, 137.2, 135.8, 132.0, 129.2, 128.5, 128.0, 127.9, 85.8, 80.1, 73.4, 67.5, 63.0, 58.5, 58.3; FTIR (neat) 3393, 3049, 2976, 1735, 1717, 1653, 1391, 1369 $cm^{-1}$; HRMS $(M+NH_4)^+$ calcd for $C_{27}H_{44}N_3O_9S$ 586.2798, found 586.2784.

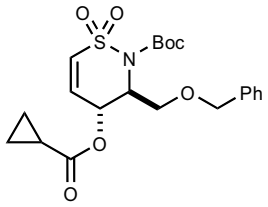
**1, 2-thiazine-*N*-carboxylic acid-3, 4-dihydro-(3*S*)-[(phenylmethoxy)methyl]-(4*S*)-isobutanoate -1, 1-dimethylethyl ester-1, 1-dioxide (2.40)**




To a solution of sultam **2.11** (10.7 mg, 0.029 mmol), DMAP (1.0 mg, 0.0087 mmol) and isovaleric acid (3.5 mg, 0.035 mmol, 3.8 μL) in $CH_2Cl_2$ (0.1 mL) was added a solution of OACC (19 mg, 0.046 mmol) in $CH_2Cl_2$ (0.2 mL) and the reaction stirred at rt for 12 h. Once complete, MP-Carbonate resin (6.5 mg) was added to the reaction mixture and the solution stirred at rt for 2 h. The solvent was removed, silica gel was added and the product filtered via $SiO_2$ plug with 100% EtOAc. The solvent was removed under reduced pressure to afford 13 mg (100 %) of **2.40** as a clear oil.

**Analytical data for 2.40:** TLC $R_f$ = 0.70 (1.5:1 hexanes/EtOAc); $[\alpha]_D^{25}$ = -119.7 (*c* = 0.68, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.34-7.29 (m, 5H), 6.49 (d, *J* = 10.5 Hz, 1H), 6.46 (ddd, *J* = 10.5, 5.0, 1.5 Hz, 1H), 5.36 (dd, *J* = 5.5, 2.0 Hz, 1H), 4.99 (dddd, *J* = 7.5, 7.5, 1.5, 1.5 Hz, 1H), 4.60 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 3.71 (d, *J* = 8.0 Hz, 2H), 2.23 (d, *J* = 7.5 Hz, 2H), 2.12-2.05 (m, 1H), 1.53 (s, 9H), 0.95 (d, *J* = 5.5 Hz, 3H), 0.95 (d, *J* = 5.5 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 172.1, 150.7, 137.3, 131.6, 129.9, 128.5, 127.9, 127.9, 85.6, 73.4, 67.6, 61.9, 58.4, 42.9, 28.0, 25.7, 22.3, 22.3; FTIR (neat) 2960, 2932, 1736, 1647, 1456, 1371 $cm^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{22}H_{31}NO_7SNa$ 476.1719, found 476.1704.

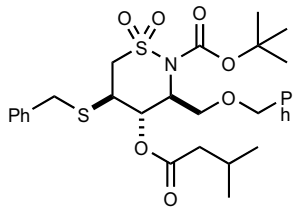
**1, 2-thiazine-*N*-carboxylic acid-3, 4-dihydro-(3*S*)-[(phenylmethoxy)methyl]-(4*S*)-cyclopropanoate -1, 1-dimethylethyl ester-1, 1-dioxide (2.41)**




In a procedure similar to the preparation of **2.40**, a solution of sultam **2.11** (11.0 mg, 0.030 mmol), DMAP (1.0 mg, 0.009 mmol) and cyclopropane carboxylic acid (3.0 mg, 0.036 mmol, 2.8 μL) in $CH_2Cl_2$ (0.1 mL) was subjected to the coupling reaction with OACC (19.0 mg, 0.048 mmol) in $CH_2Cl_2$ (0.2 mL) to afford 13 mg (100%) of **2.41** as a clear oil.

**Analytical data for 2.41:** TLC $R_f$ = 0.51 (1.5:1 hexanes/EtOAc); $[\alpha]_D^{25}$ = -137.3 (*c* = 0.675, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.34-7.28 (m, 5H), 6.49 (d, *J* = 10.5 Hz, 1H), 6.46 (ddd, *J* = 10.5, 5.0, 1.5 Hz 1H), 5.34 (dd, *J* = 5.0, 1.5 Hz, 1H), 4.99 (dddd, *J* = 7.0, 7.0, 1.5, 1.5 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 3.70 (d, *J* = 8.0 Hz, 2H), 1.69-1.64 (m, 1H), 1.54 (s, 9H), 1.03 (dd, *J* = 8.0, 5.0 Hz, 2H), 0.92 (dd, *J* = 8.0, 3.0 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 172.9, 149.7, 136.3, 130.4, 128.9, 127.4, 126.9, 126.9, 84.6, 72.3, 66.6, 61.0, 57.4, 26.9, 11.7, 8.2, 8.2; FTIR (neat) 3043, 2979, 2932, 2870, 1734, 1606, 1456 $cm^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{21}H_{27}NO_7SNa$ 460.1406, found 460.1394.

**1,2-thiazine-*N*-carboxylic acid-3,4,5,6-tetrahydro-(3*S*)-[(phenylmethoxy)methyl]-(4*R*)-(3-methylbutanoate)-(5*R*)-benzylthio-1,1-dimethylethyl ester-1,1-dioxide (2.42)**

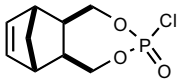


In a procedure similar to the preparation of **2.40**, sultam **2.11** (11.0 mg, 0.030 mmol) in $CH_2Cl_2$ (0.1 mL), DMAP (1.2 mg, 0.009 mmol) and isovaleric acid (3.4 mg, 0.036 mmol, 4 μL) were subjected to OACC coupling with OACC (19 mg, 0.048 mmol) in $CH_2Cl_2$ (0.20 mL). After the coupling event and scavenging of excess acid with MP-carbonate, the product was filtered via silica plug (100 % EtOAc) and the solvent removed under reduced pressure. This coupling product was dissolved in $CH_2Cl_2$ (0.3 mL) followed by the addition of BnSH (4.09 mg, 0.033 mmol, 4μL) and $Et_3N$ (0.6 mg, 0.006 mmol, 1 μL). The reaction was stirred at reflux for 12 h. OBAC (2 mg) was added to scavenge the excess thiol and the reaction heated at reflux for 4 h. Flash chromatography ($SiO_2$, 5:1 Hexane/EtOAc) afforded 15.7 mg (91%) of diversified sultam **2.42** as an inseparable mixture of diastereomers (dr ~ 6:1) as a clear oil.

**Analytical data for 2.42:** TLC $R_f$ = 0.53 (2:1 Hexanes/EtOAc); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.37-7.27 (m, 10H), 5.18 (dd, *J* = 7.5, 2.0 Hz, 1H), 4.72 (ddd, *J* = 7.0, 5.5, 2.0 Hz, 1H), 4.55 (s, 2H), 3.88 (dd, *J* = 10.5, 6.5 Hz, 1H), 3.82 (dd, *J* = 10.5, 5.5 Hz, 1H), 3.80 (d, *J* = 13.5 Hz, 1H), 3.75 (d, *J* = 13.5 Hz, 1H), 3.57 (dd, *J* = 14.0, 10.0 Hz, 1H), 3.37 (dd, *J* = 14.0, 4.0 Hz, 1H), 3.31 (ddd, *J* = 11.0, 7.5, 4.0 Hz, 1h), 2.19 (dd, *J*

= 8.0, 7.5 Hz, 2H), 2.10-2.05 (m, 1H), 1.49 (s, 9H), 0.96 (d, *J* = 7.0 Hz, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 172.0, 150.9, 137.3, 136.8, 128.8, 128.7, 128.3, 127.8, 127.7, 127.5, 85.0, 73.4, 70.1, 70.0, 61.7, 53.1, 43.1, 41.4, 36.1, 27.8, 25.6, 22.3, 22.3; FTIR (neat) 3030, 2960, 2932, 2872 1732, 1606, 1454, 1138 $cm^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{29}H_{39}NO_7S_2Na$ 600.2066, found 600.2083.

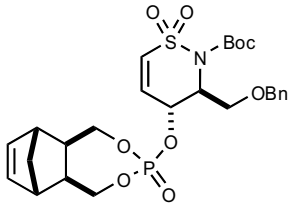
**5-norbornene-2-*exo*,3-*exo*-dimethyl phosphorochloridate (2.43)**



To a solution of 5-norbornene-2-*exo*,*3*-exo-dimethanol (159 mg, 1.03 mmol), DMAP (15 mg, 0.123 mmol) and $Et_3N$ (313 mg, 3.09 mmol, 0.43 mL).in $CH_2Cl_2$ (5.2 mL) was added freshly distilled $POCl_3$ (174 mg, 1.13 mmol, 106 μL) at 0 °C and the reaction stirred at rt for 1 h. The crude product was concentrated under reduced pressure, filtered through celite, followed by flash chromatography ($SiO_2$, 2:1 Heptane/EtOAc) to afford 121 mg (50%) of **2.43** as an inseparable mixture of diastereomers (dr = 2.8:1) as a white solid.

**Analytical data for 2.43 (major diastereomer):** TLC $R_f$ = 0.52 (1:1 Hexanes/EtOAc);$^1$H NMR (400 MHz, $CDCl_3$) δ 6.26 (t, *J* = 1.6 Hz, 2H), 4.47-4.41 (m, 1H), 4.39 (dd, *J* = 12.4, 4.4 Hz, 1H), 4.31 (dd, *J* = 12.4, 4.0 Hz, 1H), 4.18-4.15 (m, 1H), 2.62 (t, *J* = 1.6 Hz, 2H), 2.26-2.19 (m, 2H), 1.45-1.42 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 137.8, 71.1 (d, $J_{CP}$ = 36.0 Hz), 46.2, 45.2, 42.0; $^{31}$P NMR (400 MHz, $CDCl_3$) δ 2.2; FTIR (neat) 3076, 2978, 1299, 1253, 1045 $cm^{-1}$. HRMS $(M+H)^+$ calcd for $C_9H_{13}ClO_3P$ 235.0291, found 235.0286.

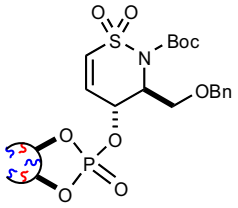
**Norbornenyl-Tagged Sultam (2.44)**



To a solution of sultam **2.11** (108 mg, 0.29 mmol) in $CH_2Cl_2$ (0.58 mL) was added *N*-methylimidazole (71 mg, 0.87 mmol, 69 μL) and norbornenyl monochloride **2.43** (137 mg, 0.87 mmol) and the reaction stirred at rt for 6-12 h. Flash chromatography ($SiO_2$, 1:1 Hexanes/EtOAc) afforded 160 mg (97%) of tagged sultam **2.44** as a mixture of diastereomers (dr = 2.8:1) as a white solid.

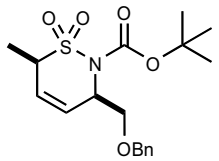
**Analytical data for 2.44:** TLC $R_f$ = 0.18 (1:1 Hexanes/EtOAc); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.36-7.30 (m, 5H), 6.59 (ddd, *J* = 10.5, 5.5, 1.5 Hz, 1H), 6.53 (d, 10.5 Hz, 1H), 6.22 (dd, *J* = 9.0, 1.0 Hz, 2H), 5.11-5.09 (m, 1H), 5.08-5.04 (m, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 11.5 Hz, 1H), 4.44-4.46 (m, 2H), 4.25-4.13 (m, 2H), 3.73-3.66 (m, 2H), 2.59-2.53 (m, 2H), 2.20-2.13 (m, 2H), 1.52 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 150.9, 137.4, 137.3, 137.1, 131.7, 130.1 (d, $J_{CP}$ = 10.0 Hz), 128.5, 128.0, 127.9, 85.8, 73.5, 70.7 (d, $J_{CP}$ = 20.0 Hz), 69.9 (d, $J_{CP}$ = 35.0 Hz), 67.5, 64.8 (d, $J_{CP}$ = 20.0 Hz), 59.6 (d, $J_{CP}$ = 25.0 Hz), 44.9 (d, $J_{CP}$ = 15.0 Hz), 44.8, 43.4, 42.0, 41.9 (d, $J_{CP}$ = 15.0 Hz), 27.9; 31P (400 MHz, CDCl3) δ -5.1, -16.4; FTIR (neat) 3050, 2972, 1732, 1637, 1371, 1337, 1167, 1135, 1015 $cm^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{26}H_{34}NO_9PSNa$ 590.1590, found 590.1584.

**ROMP Sultam (2.45)**




To a stirring solution of norbornenyl tagged sultam **2.44** (58 mg, 0.102 mmol) in degassed $CH_2Cl_2$ (1.0 mL) was added 5 mol % (4.0 mg, 0.005 mmol) of Grubbs first generation catalyst (Cat.-B) in one portion. The reaction was refluxed under argon and monitored by TLC analysis. Once polymerization was complete (~ 3 h), the reaction was quenched by the addition of ethyl vinyl ether (2 mL). The mixture was reduced to 1/3 of the original volume and 10 mL of diethyl ether were added to induce precipitation. Filtration yielded 47 mg (81%) as a gray solid. This product was immediately used for the organocuprate realease strategy.

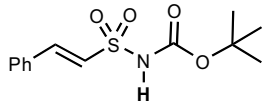
**1,2-thiazine-*N*-carboxylic acid-3,6-dihydro-(3*R*)-[(phenylmethoxy)methyl]-(6*R*)-methyl- 1,1-dimethylethyl ester-1,1-dioxide (2.46)**




In a procedure similar to the preparation of sultam **2.24**, ROMP sultam **2.45** (26 mg, 0.046 mmol) was subjected to dimethyl cuprate addition with CuCN·2LiCl (0.46 mmol, 0.46 mL) and $Me_2Zn$ (0.46 mmol, 0.38 mL) in dry THF (0.46 mL) to afford after flash chromatography ($SiO_2$, 5:1 Hexane/EtOAc) 11mg (65%) of sultam **2.46** as a light-yellow oil.

**Analytical data for 2.46:** TLC $R_f$ = 0.44 (2:1 Hexanes/EtOAc); $[\alpha]_D^{25}$ = +85.4 (*c* = 0.35, $CHCl_3$); $^1H$ (500 MHz, $CDCl_3$) δ 7.33-7.28 (m, 5H), 5.90 (dd, *J* = 11.0, 2.5 Hz, 1H), 5.49 (d, *J* = 11.0 Hz, 1H), 5.28 (m, 1H), 4.55 (s, 2H), 4.02-4.00 (m, 1H), 3.81-3.74 (m, 2H), 1.49 (s, 12H); $^{13}C$ (125 MHz, $CDCl_3$) δ 150.7, 137.9, 128.4, 127.7, 125.7, 124.7, 84.5, 73.3, 70.9, 60.2, 54.7, 27.9, 13.5; FTIR (neat) 3063, 2935, 1724, 1454, 1363, 1169 $cm^{-1}$; HRMS $(M+NH_4)^+$ calcd for $C_{18}H_{29}N_2O_5S$ 385.1797, found 385.1815.

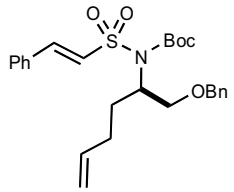
**(*E*)-*tert*-butyl styrylsulfonylcarbamate (2.49)**



To a solution of (*E*)-2-phenylethenesulfonamide (1.0 g, 5.46 mmol) in $CH_2Cl_2$ (6.8 mL) containing DMAP (66 mg, 0.55 mmol) and $Et_3N$ 607 mg, 6.0 mmol, 0.84 mL) at rt was added a solution of $BocO_2$ (1.37 g, 6.27 mmol, 1.44 mL) in $CH_2Cl_2$ (10.9 mL) dropwise with stirring over 20 min. The reaction was stirred for 2 h at rt, followed by removal of the solvent under reduced pressure. The crude product was treated with EtOAc (80 mL) and 1N HCl (53 mL) and the organic layer washed successively with water (50 mL) and brine (50 mL). The water layer was washed with $CH_2Cl_2$ (4 × 50 mL), the organic layers combined, dried over $Na_2SO_4$, filtered and concentrated under reduced pressure. The product was heated in heptane (20 mL), cooled down to rt and filtered to give 1.46 g (94%) of styrylsulfonylcarbamate **2.49** as an ivory solid.

**Analytical data for 2.49:** TLC $R_f$ = 0.51(1:1 Hexanes/EtOAc); Mp = 160-166 °C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 15.4 Hz, 1H), 7.54-7.52 (m, 2H), 7.46-7.41 (m, 3H), 7.20 (s, 1H, N-H), 7.00 (d, *J* = 15.4 Hz, 1H), 1.48 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 149.3, 144.6, 132.1, 131.5, 129.2, 128.7, 123.9, 84.3, 28.0; FTIR (neat) 3246, 1736, 1614, 1576 cm$^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{13}H_{17}NO_4SNa$ 306.0776, found 306.0769.

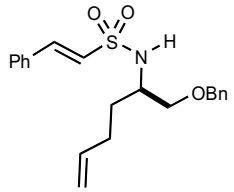
**(*R*,*E*)-*tert*-butyl 1-(benzyloxy)hex-5-en-2-yl(styrylsulfonyl)carbamate (2.51)**




In a procedure similar to the preparation of sulfonamide **2.5**, a solution of sulfamoyl carbamate **2.49** (1.42 g, 5.01 mmol) in THF (3.2 mL) was subjected to the Mitsunobu reaction in the presence of secondary alcohol **2.50** (1.03g, 5.01 mmol), $PPh_3$ (1.71g, 5.51 mmol) and DIAD (1.11 g, 5.51 mmol, 1.07 mL) to yield after flash chromatography ($SiO_2$, 10:1 Hexane/EtOAc) 1.93 g (82%) of sulfamoyl carbamate **2.51** as a yellow oil.

**Analytical data for 2.51:** TLC $R_f$ = 0.49 (3:1 Hexanes/EtOAc); $[\alpha]_D^{25}$ = -9.1 (*c* = 1.06, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 15.5 Hz, 1H), 7.41-7.37 (m, 1H), 7.33-7.27 (m, 7H), 7.20 (d, *J* = 7.4 Hz, 2H), 6.98 (d, *J* = 15.5 Hz, 1H), 5.86 (dddd, *J* = 16.8, 10.2, 6.5, 6.3 Hz, 1H), 5.08 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.01 (dd, *J* = 10.2, 1.0 Hz, 1H), 4.74-4.66 (m, 1H), 4.58 (d, *J* = 11.6 Hz, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 3.96 (dd, *J* = 9.8, 9.8 Hz, 1H), 3.56 (dd, *J* = 9.8, 5.1 Hz, 1H), 2.28-2.16 (m, 2H), 2.14-2.03 (m, 1H), 1.73-1.63 (m, 1H), 1.47 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 150.7, 142.2, 137.7, 137.2, 132.1, 130.5, 128.7, 128.1, 127.9, 127.3, 127.2, 125.2, 114.9, 83.7, 72.7, 69.9, 58.0, 30.2, 29.1, 27.7; FTIR (neat) 3070, 2980, 1726, 1639, 1616, 1578, 1450, 1353, 1145 $cm^{-1}$; HRMS $(M+H)^+$ calcd for $C_{26}H_{34}NO_5S$ 472.2158, found 472.2159.

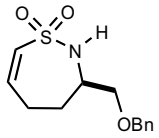
**(*R*,*E*)-*N*-(1-(benzyloxy)hex-5-en-2-yl)-2-phenylethenesulfonamide (2.52)**




In a procedure similar to the preparation of sulfonamide **2.7**, a solution of sulfamoyl carbamate **2.51** (115 mg, 0.24 mmol) in $CH_2Cl_2$ (2.0 mL) was treated with TFA (0.5 mL) to yield after aqueous workup and flash chromatography ($SiO_2$, 2:1 Heptane/EtOAc) 91 mg (100%) of sulfonamide **2.52** as an ivory solid.

**Analytical data for 2.52:** TLC $R_f$ = 0.45 (2:1 Hexanes/EtOAc); Mp = 40-43 °C; $[\alpha]_D^{25}$ = +18.0 (*c* = 1.135, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 15.4 Hz, 1H), 7.39-7.27 (m, 10H), 6.67 (d, *J* = 15.4 Hz, 1H), 5.77 (dddd, *J* = 16.8, 10.2, 6.6, 6.6 Hz, 1H), 5.00 (dd, *J* = 17.1, 1.6 Hz, 1H), 4.96 (dd, *J* = 10.2, 1.3 Hz, 1H), 4.62 (d, *J* = 8.3 Hz, 1H), 4.50 (s, 2H), 3.53 (dd, *J* = 8.8, 3.4 Hz, 1H), 3.49-3.42 (m, 2H), 2.22-2.06 (m, 2H), 1.69 (q, J = 7.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 140.5, 137.6, 137.5, 132.6, 130.5, 129.0, 128.4, 128.1, 127.8, 127.7, 126.2, 115.3, 73.2, 71.7, 53.3, 31.9, 29.8; FTIR (neat) 3279, 3063, 2928, 1622, 1448, 1363, 1150 $cm^{-1}$; HRMS $(M+H)^+$ calcd for $C_{21}H_{26}NO_3S$ 372.1633, found 372.1643.

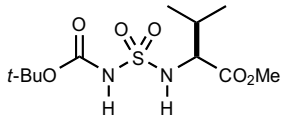
**1,2-thiazepin-3,4,5-trihydro-(3*R*)-[(phenylmethoxy)methyl]-1,1-dioxide (2.53)**




A solution of **s**ulfonamide **2.52** (361 mg, 0.97 mmol) in DCE (194 mL) was subjected to RCM with Grubbs second generation catalyst (Cat. C) (5 mol %, 41 mg, 0.049 mmol) at reflux to afford after flash chromatography ($SiO_2$, 3:1 Heptane/EtOAc) 224 mg (86%) of vinylic sultam **2.53** as a yellow oil.

**Analytical data for 2.53:** TLC $R_f$ = 0.28 (1:1 Hexanes/EtOAc); $[\alpha]_D^{25}$ = -1.73 (*c* = 0.925, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.38-7.29 (m, 5H), 6.61 (dd, *J* = 11.1, 1.9 Hz, 1H), 6.36 (ddd, *J* =11.1, 7.2, 5.5 Hz, 1H), 4.89 (d, *J* = 7.9 Hz, 1H), 4.55 (d, *J* = 11.8 Hz, 1H), 4.50 (d, *J* = 11.8 Hz, 1H), 3.80-3.73 (m, 1H), 3.64-3.55 (m, 2H), 2.65-2.57 (m, 2H), 2.04-1.99 (m, 1H), 1.94-1.87 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 139.2, 137.4, 135.0, 128.2, 127.6, 127.5, 73.0, 72.5, 53.8, 28.5, 25.9; FTIR (neat) 3265, 3059, 3030, 2926, 1624, 1496, 1452, 1363 $cm^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{13}H_{17}NO_3SNa$ 290.0827, found 290.0829.

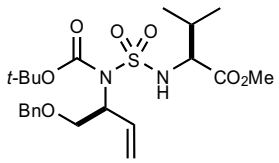
**(*S*)-methyl 2-(*N*-(tert-butoxycarbonyl)sulfamoylamino)-3-methylbutanoate (3.34)**




To a stirring solution of chlorosulfonyl isocyanate (1.23 mL, 14.1 mmol) and $CH_2Cl_2$ (40 mL) at 0 °C in a 250 mL round bottom flask was added a solution of *t*-BuOH (1.0 M, 1.35 mL, 14.1 mmol) in $CH_2Cl_2$ dropwise over a period of 10 min. The resulting solution was transferred via cannula to a mixture of H-Val-OMe·HCl (2.37 g, 14.1 mmol) and $Et_3N$ (3.94 mL, 28.3 mmol) in $CH_2Cl_2$ (40 mL) at 0 °C. The slurry was allowed to warm to rt and stirred for an additional 2.5 h. The salts were filtered, the organic portion was washed with $H_2O$ (2×), brine (2×), and dried over $Na_2SO_4$. The mixture was filtered and concentrated under reduced pressure to yield 4.19 g (96%) of sulfamide **3.34** as a pure white solid.

**Analytical data for 3.34:** TLC $R_f$ = 0.42 (2:1 Hexanes/EtOAc); Mp = 128-129 °C; $[\alpha]_D^{25}$ = +40.6 (*c* = 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 1H), 5.54 (d, *J* = 9.2 Hz, 1H), 4.04 (dd, *J* = 9.2, 4.9 Hz, 1H), 3.76 (s, 3H), 2.18-2.10 (m, 1H), 1.49 (s, 9H), 1.18 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.9, 149.9, 83.8, 62.1, 52.4, 31.4, 27.9, 18.9, 17.3; FTIR (neat) 3268, 1742, 1451, 1400, 1371, 1146 $cm^{-1}$; HRMS $(M+H)^+$ calcd for $C_{11}H_{23}N_2O_6S$ 311.1277, found 311.1266.

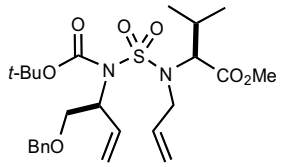
***N*-[(1*S*)-1-(1-Benzyloxy)methyl-2-propenyl]-*N*-[(1,1-dimethylethoxy)carbonyl]-*N*'-[(1*S*)-1-(1-methylethyl)-2-methoxycarbonyl]-sulfamide (3.36)**.




To a stirring solution of sulfamoyl carbamate **3.34** (400 mg, 1.30 mmol) in THF (1.0 mL) at rt under argon was added $PPh_3$ (341 mg, 1.3 mmol) and alcohol **3.35** (231 mg, 1.30 mmol) followed by dropwise addition of DIAD (256 mL, 1.3 mmol). The solution was stirred for 8 h and the solvent removed under reduced pressure. Flash chromatography (20:1, heptanes/EtOAc) afforded 403 mg (67%, 6:1 mixture of regioisomers) of the sulfamoyl carbamate **3.36** as a clear yellow oil.

**Analytical data for 3.36:** TLC $R_f$ = 0.30 (3:1 heptane/EtOAc); $[\alpha]_D^{25}$ = +33.4 (*c* = 1.246, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5H), 6.00–5.93 (m, 2H), 5.28 (dd, *J* = 17.4, 1.0 Hz, 1H), 5.21 (dd, *J* = 10.4, 1.0 Hz, 1H), 5.10 (dd, *J* = 14.4,7.1 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.57 (d, *J* = 12.0 Hz,1H), 4.03 (dd, *J* = 8.3, 4.4 Hz, 1H), 3.93 (dd, *J* = 10.0, 8.8 Hz,1H), 3.67 (s, 3H), 3.65 (dd, *J* = 10.0, 6.0 Hz, 1H), 2.14–2.06 (m, 1H), 1.52 (s, 9H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.9 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.4, 151.2, 137.9, 134.0, 128.3, 127.7, 127.6, 118.4, 84.4, 72.8, 70.1, 61.8, 60.4, 52.1, 31.8, 27.9, 18.8, 17.1; FTIR (neat) 3321, 3064, 1741, 1724, 1643, 1605, 1495, 1369,1151 $cm^{-1}$; HRMS $(M+H)^+$ calcd for $C_{22}H_{35}N_2O_7S$ 471.2165, found 471.2155.

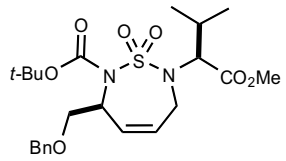
***N*-[(1*S*)-1-(1-Benzyloxy)methyl-2-propenyl]-*N*-[(1,1-dimethylethoxy)carbonyl]-*N*'-[(1S)-1-(1-methylethyl)-2-methoxycarbonyl]-*N*'-2-propenyl-sulfamide (3.37).**




To a stirring solution of sulfamide **3.36** (119 mg, 0.25 mmol) in $CH_3CN$ (3 mL) in a pressure tube was added $K_2CO_3$ (173 mg, 1.25 mmol) and allyl bromide (216 mL, 2.5 mmol). The pressure tube was heated to 70 °C for 12 h. The resulting yellow-orange mixture was filtered by suction, and the solvent removed under reduced pressure. Flash chromatography (8:1 heptanes/EtOAc) afforded 120 mg (92%) of diene **3.37** as a clear yellow oil.

**Analytical data for 3.37:** TLC $R_f$ = 0.41 (3:1 heptane/EtOAc); $[\alpha]_D^{25}$ =-37.9 (*c* = 0.98, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 5H), 6.03 (dddd, *J* = 17.4, 10.1, 5.3, 5.3 Hz, 1H), 5.97 (ddd, *J* = 17.0, 10.5, 6.1 Hz, 1H), 5.29 (d, *J* = 17.4 Hz, 1H), 5.20 (d, *J* = 10.5 Hz, 1H), 5.15 (dd, *J* = 11.5, 1.0 Hz, 1H), 5.10-5.03 (m, 1H), 5.04 (dd, *J* = 10.0, 1.0 Hz, 1H), 4.57 (d, *J* = 12.2 Hz, 1H) 4.54 (d, *J* = 12.0 Hz, 1H), 4.30 (dd, *J* = 16.8, 7.7 Hz, 1H), 4.24 (dd, *J* = 16.9, 5.2 Hz, 1H), 4.14 (d, *J* = 10.5 Hz, 1H), 3.89 (dd, *J* = 9.7, 7.7 Hz, 1H), 3.68 (s, 3H), 3.67 (dd, *J* = 9.9, 6.8 Hz, 1H), 2.16-2.04 (m, 1H), 1.42 (s, 9H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.4, 151.1, 137.8, 135.8, 134.5, 128.2, 127.6, 127.5, 117.6, 116.6, 83.6, 72.7, 70.6, 66.2, 60.8, 51.2, 48.8, 28.8, 27.9, 19.6, 19.2; FTIR (neat) 3081, 1726, 1640, 1367, 1140 $cm^{-1}$; HRMS $(M+H)^+$ calcd for $C_{25}H_{39}N_2O_7S$ 511.2478, found 511.2460.

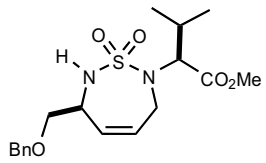
**2-(2*S*)-[(6*S*)-(6-Benzyloxymethyl-7-(1,1-dimethylethoxy)carbonyl-1,1-dioxo-1,3,6,7-tetrahydro-1,2,7-thiadiazepin-2-yl)]-3-methyl-butyric acid methyl ester (3.38).**




To a stirring solution of allylated sulfamide **3.37** (115 mg, 0.22 mmol) in degassed $CH_2Cl_2$ (3 mL) in a pressure tube was added $(ImesH_2)(PCy_3)(Cl)_2Ru{=}CHPh$ (9 mg, 0.011 mmol, 5 mol%). The solution was stirred at reflux for 3 h and opened up to air. DMSO (40 mL) was added the mixture stirred for 12 h, and the solvent concentrated. Flash chromatography (10:1 heptanes/EtOAc) yielded 104 mg (96%) of cyclic sulfamide **3.38** as a clear yellow oil.

**Analytical data for 3.38:** TLC $R_f$ = 0.32 (3:1 heptanes/EtOAc); $[\alpha]_D^{25}$ =-59.8 (*c* = 0.88, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.35–7.27 (m, 5H), 5.78-5.72 (m, 1H), 5.55-5.50 (m, 1H), 5.04 (bs, 1H), 4.57 (s, 2H), 4.28 (d, *J* = 10.4 Hz, 1H), 4.15-4.10 (m, 1H), 3.86-3.79 (m, 3H), 3.64 (s, 3H), 2.20-2.11 (m, 1H), 1.49 (s, 9H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.4, 151.1, 138.0, 128.5, 128.3, 127.6, 127.6, 125.4, 84.0, 72.8, 71.6, 65.5, 55.5, 52.0, 43.4, 28.3, 27.8, 19.2, 19.1; FTIR (neat) 3030, 1741, 1604, 1369, 1154 $cm^{-1}$; HRMS $(M+H)^+$ calcd for $C_{23}H_{35}N_2O_7S$ 483.2165, found 483.2156.

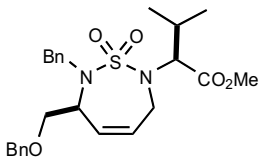
**2-(2*S*)-[(6*S*)-(6-Benzyloxymethyl-1,1-dioxo-1,3,6,7-tetrahydro-1,2,7-thiadiazepin-2-yl)]-3-methylbutyric acid methyl ester (3.39).**




The cyclic sulfamoyl carbamate **3.38** (64.6 mg, 0.13 mmol) was dissolved in TFA/$CH_2Cl_2$ (1:1). After 30 min. the reaction was quenched with saturated $NaHCO_3$ (10 mL) and extracted with $CH_2Cl_2$ (4 × 15 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford 49 mg (96%) of sulfamide **3.39** as a yellow oil.

**Analytical data for 3.39:** TLC $R_f$ = 0.21 (3:1 heptane/EtOAc); $[\alpha]_D^{25}$ = -45.1 (*c* = 1.025, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.38-7.30 (m, 5H), 5.64 (bs, 2H), 5.14 (d, *J* = 10.2 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 4.20-4.15 (m, 2H), 4.11 (d, *J* = 11.0 Hz, 1H), 3.76-3.70 (m, 1H), 3.65 (s, 3H), 3.60-3.58 (m, 2H), 2.21-2.12 (m, 1H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.0, 137.4, 130.9, 128.6, 128.5, 128.0, 127.8, 73.5, 72.0, 66.1, 51.8, 50.9, 41.0, 27.4, 19.2, 19.0; FTIR (neat) 3284, 3029, 1738, 1603, 1333, 1150 $cm^{-1}$; HRMS $(M+H)^+$ calcd for $C_{18}H_{27}N_2O_5S$ 383.1641, found 383.1662.

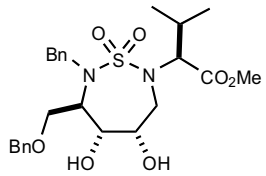
**2-(2*S*)-[(6*S*)-(7-Benzyl-6-benzyloxymethyl-1,1-dioxo-1,3,6,7-tetrahydro-1,2,7-thiadiazepin-2-yl)]-3-methyl-butyric acid methyl ester (3.40).**




To a stirring solution of cyclic sulfamide **3.39** (49 mg, 0.13 mmol) in $CH_3CN$ (5 mL) in a pressure tube was added $K_2CO_3$ (90 mg, 0.65 mmol) and benzyl bromide (150 μL, 1.3 mmol). The reaction was heated to 70 °C for 12 h, filtered via suction filtration, and purified by column chromatography (10:1 heptane/EtOAc) to afford 54 mg (89%) of the benzylated sulfamide **3.40** as a yellow oil.

**Analytical data for 3.40:** TLC $R_f$ = 0.29 (3:1 heptanes/EtOAc); $[\alpha]_D^{25}$ = -68.5 (*c* = 0.80, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.41-7.18 (m, 10H), 5.82-5.78 (m, 1H), 5.75-5.72 (m, 1H), 4.66-4.63 (m, 2H), 4.31 (s, 1H), 4.28 (d, *J* = 3.7 Hz, 1H), 4.22 (d, *J* = 11.9 Hz, 1H), 4.20 (d, *J* = 11.0 Hz, 1H), 3.99-3.94 (m, 1H), 3.82-3.76 (m, 1H), 3.72 (s, 3H), 3.54 (dd, *J* = 9.5, 6.0 Hz, 1H), 3.42 (dd, *J* = 9.5, 7.2 Hz, 1H), 2.22-2.14 (m, 1H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.5 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.8, 138.3, 137.6, 128.8, 128.4, 128.3, 128.3, 128.2, 127.5, 127.1, 126.9, 72.9, 70.9, 65.8, 55.4, 51.8, 51.0, 40.6, 27.8, 19.2, 19.1; FTIR (neat) 2962, 1740, 1496, 1454, 1334, 1150 $cm^{-1}$; HRMS $(M+H)^+$ calcd for $C_{25}H_{33}N_2O_5S$ 473.2110, found 473.2110.

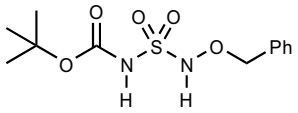
**2-(2*S*)-[(4*S*,5*R*,6*R*)-(7-Benzyl-6-benzyloxymethyl-4,5-dihydroxy-1,1-dioxo-1,3,6,7-tetrahydro-1,2,7-thiadiazepin-2-yl)]-3-methyl-butyric acid methyl ester (3.41).**




In a procedure similar to the preparation of the sultam diol **2.9**, sulfamide **3.40** (93 mg, 0.200 mmol) was subjected to dihydroxylation conditions NMO·$H_2O$ (28 mg, 0.24 mmol), citric acid (84 mg, 0.40 mmol) and $OsO_4$ (75 mL, 0.012 mmol, 6 mol%). Flash chromatography (1:1 heptane/EtOAc) produced 70 mg (70%) of the sulfamide diol **3.41** as a clear oil.

**Analytical data for 3.41:** TLC $R_f$ = 0.49 (1:3 heptane/EtOAc); $[\alpha]_D^{25}$ -37.5 (*c* = 0.995, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.39-7.09 (m, 10H), 4.58 (d, *J* = 14.2 Hz, 1H), 4.39 (d, *J* = 7.7 Hz, 1H), 4.35 (d, *J* = 10.3 Hz, 1H), 4.29 (d, *J* = 11.8 Hz, 1H), 4.25 (d, *J* = 11.8 Hz, 1H), 4.22-4.20 (m, 1H), 4.05 (d, *J* = 14.2 Hz, 1H), 3.88 (d, *J* = 1.3 Hz, 1H), 3.84 (dd, *J* = 10.2, 9.1 Hz, 1H), 3.78 (s, 3H), 3.69 (dd, *J* = 14.5, 5.6 Hz, 1H), 3.42 (d, *J* = 14.3 Hz, 1H), 3.29-3.23 (m, 2H), 3.15 (dd, *J* = 9.0, 4.8 Hz, 1H), 2.21-2.13 (m, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.97 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 172.9, 136.9, 136.6, 128.9, 128.5, 128.4, 127.9, 127.8, 127.4, 78.4, 74.1, 73.3, 73.2, 67.4, 59.2, 55.1, 52.1, 45.8, 28.9, 19.3, 19.2; FTIR (neat) 3468, 1739, 1345, 1140 cm$^{-1}$; HRMS $(M+H)^+$ calcd for $C_{25}H_{35}N_2O_7S$ 507.2165, found 507.2152.

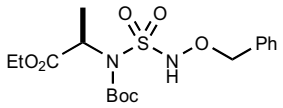
***tert*-butyl *N*-(benzyloxy)sulfamoylcarbamate 3.42**



To a cold (0 °C) solution of CSI (17.8 mmol, 2.52 g) in $CH_2Cl_2$ (3 mL) was added *tert*-butyl alcohol (17.8 mmol, 1.32g) dropwise via syringe and the solution stirred for 1 h at that temperature. This solution was then transferred via cannula to a cold (0 °C) solution of *O*-benzyl hydroxylamine hydrochloride (17.8 mmol, 2.84 g) in $CH_2Cl_2$ (25 mL) and $Et_3N$ (35.6 mmol, 3.60 g). The reaction was stirred until it slowly reached rt. Upon completion, water (100 mL) was added and the crude mixture extracted with $CH_2Cl_2$ (4 × 100 mL). The organic layers were combined, dried with $Na_2SO_4$, filtered and concentrated under reduced pressure. Flash chromatography ($SiO_2$, 10:1 Heptane/EtOAc) afforded 4.57 g (85%) of **3.42** as a white solid.

**Analytical data for 3.42:** TLC $R_f$ = 0.49 (1:1 Heptane/EtOAc); Mp = 98 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.60 (s, 1H), 7.38 (m, 5H), 4.99 (s, 2H), 1.48 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 149.7, 134.8, 129.4, 128.8, 128.5, 85.0, 79.2, 27.8; FTIR (neat) 3120, 2957, 2870, 1612, 1514, 1465, 1323, 1247, 1035, 877, 737, 700 $cm^{-1}$; HRMS $(M + Na)^+$ calcd for $C_{12}H_{18}N_2O_5Na$ 325.0834, found 325.0842.

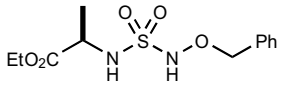
**(*R*)-ethyl-2-((*N*-(benzyloxy)sulfamoyl)(*tert*-butoxycarbonyl)amino)propanoate (3.43)**




To a solution of sulfamoyl carbamate **3.42** (4.20 mmol, 1.26 g), (*S*)-ethyl lactate (4.2 mmol, 496 mg) and $PPh_3$ (4.20 mmol, 1.10 g) in THF (4.5 mL) was added DIAD (4.2 mmol, 849 mg) dropwise via syringe. The reaction was stirred at rt for approximately 1 h. Flash chromatography ($SiO_2$, 10:1 Heptane/EtOAc) provided 1.07g (64%) of **3.43** as a clear yellow oil.

**Analytical data for 3.43:** TLC $R_f$ = 0.58 (1:1 Heptane/EtOAc); $[\alpha]_D^{25}$ = -40.0 (*c* = 0.69, $CHCl_3$) $^1$H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H, N-H), 7.36-7.35 (m, 5H), 4.98 (s, 2H), 4.89 (q, *J* = 7.0 Hz, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 1.52 (d, *J* = 7.0 Hz, 3H), 1.46 (s, 9H), 1.20 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.6, 150.2, 134.7, 129.2, 128.3, 128.2, 85.5, 78.8, 61.4, 55.6, 27.5, 15.7, 13.8; FTIR (neat) 3244, 2982, 1744, 1724, 1620, 1456 $cm^{-1}$; HRMS (M+Na)+ calcd for $C_{17}H_{26}N_2O_7SNa$ 425.1359, found 425.1340.

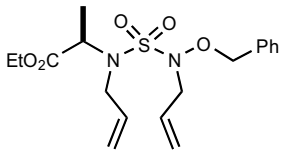
**(*R*)-ethyl 2-(*N*-(benzyloxy)sulfamoylamino)propanoate (3.44)**




To a solution of **3.43** (3.38 mmol, 1.36 g) in $CH_2Cl_2$ (2 mL) was added TFA (2 mL) dropwise via syringe. The reaction was stirred for 1 h and quenched with a saturated solution of $NaHCO_3$ (5 mL), followed by extraction with $CH_2Cl_2$ (4 × 50 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography ($SiO_2$, 6:1 Heptane/ EtOAc) afforded 1.02g (100%) of **3.44** as a light-yellow solid.

**Analytical data for 3.44:** TLC $R_f$ = 0.42 (1:1 Heptane/EtOAc); Mp = 53-56 °C; $[\alpha]_D^{25}$ = -8.57 (*c* = 1.72, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H, N-H), 7.36-7.33 (m, 5H), 5.49 (d, *J* = 8.3 Hz, 1H), 4.93 (d, *J* = 10.9 Hz. 1H), 4.88 (d, *J* = 10.9 Hz, 1H), 4.24 (quintet, *J* = 7.3 Hz, 1H), 4.17-4.09 (m, 1H), 4.05-3.97 (m, 1H), 1.42 (d, *J* = 7.3 Hz, 3H), 1.16 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.9, 135.3, 129.3, 128.6, 128.4, 78.8, 62.0, 52.9, 19.4, 13.8; FTIR (neat) 3240, 3034, 2986, 1732, 1624,1454 $cm^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{12}H_{18}N_2O_5SNa$ 325.0834, found 325.0828.

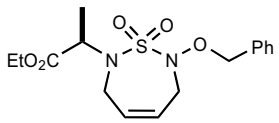
**(*R*)-ethyl 2-(allyl(*N*-allyl-*N*-(benzyloxy)sulfamoyl)amino)propanoate (3.45)**




To a solution of sulfamide **3.44** (2.0 mmol, 605 mg) in MeCN (25 mL) was added $K_2CO_3$ (10.0 mmol, 1.38 g) and allyl bromide (20.0 mmol, 2.42 g) and the reaction heated at 80 °C for 6 h. The product was filtered and purified by flash chromatography ($SiO_2$, 10:1 Heptane/EtOAc) to afford 730 mg (95%) of **3.45** as a yellow oil.

**Analytical data for 3.45:** TLC $R_f$ = 0.57 (1:1 Heptane/EtOAc); $[\alpha]_D^{25}$ = + 29.9 (*c* = 0.855, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.35-7.33 (m, 5H), 5.90 (m, 2H), 5.31 (dd, *J* = 17.2, 1.0 Hz, 1H), 5.24 (dd, *J* = 10.2, 1.0 Hz, 1H), 5.18 (dd, *J* = 17.2, 1.0 Hz, 1H), 5.11 (dd, *J* = 10.2, 1.0 Hz, 1H), 4.93 (d, *J* = 9.8 Hz, 1H), 4.86 (d, *J* = 9.7 Hz, 1H), 4.63 (q, *J* = 7.4 Hz, 1H), 4.12-4.04 (m, 2H), 3.94-3.85 (m. 2H), 1.46 (d, *J* = 7.4 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.7, 135.5, 135.16, 131.8, 129.3, 128.4, 128.2, 120.0, 117.3, 78.7, 61.1, 56.7, 55.6, 49.9, 17.0, 13.8; FTIR (neat) 3082, 2984, 1740, 1647, 1454, $cm^{-1}$; HRMS $(M+H)^+$ calcd for $C_{18}H_{27}N_2O_5S$ 383.1641, found 383.1645.

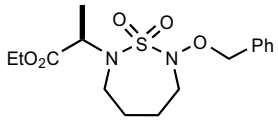
**2,3,6,7-tetrahydro-1,2,7-thiazepine-1,1-dioxo-2,7-diyl-*N*-benzyloxy-*N*'-(2*R*)-methyl ethanoic acid ethyl ester (3.46)**




To a degassed solution of bisallyl sulfamide **3.45** (0.19 mmol, 72.0 mg) in toluene (15 mL) was added Grubbs second generation catalyst (0.011 mmol, 6.0 mg) and the reaction was stirred at reflux for 4 h. The residual ruthenium was removed by addition of $NaHCO_3$ (0.275 mmol, 23.0 mg) and $C_{14}H_{12}O_4PCl$ (0.275 mmol, 52.0 mg) and refluxing for 10 h. Flash chromatography ($SiO_2$, 8:1 Heptane/EtOAc) afforded 66 mg (97%) of **3.46** as a clear yellow oil.

**Analytical data for 3.46:** TLC $R_f$ = 0.52 (1:1 Heptane/EtOAc); $[\alpha]_D^{25}$ = -7.6 (*c* = 1.48, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.37-7.32 (m. 5H), 6.03-5.99 (m, 1H), 5.67-5.64 (m, 1H), 4.95 (d, *J* = 10.9 Hz, 1H), 4.89 (d, *J* = 10.8 Hz, 1H), 4.77 (q, *J* = 7.3 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.06 (t, *J* = 16.0 Hz, 2H), 3.74-3.65 (m, 2H), 1.39 (d, *J* = 7.3 Hz, 3H), 1.26 (t, *J* = 7.5 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.8, 135.7, 133.3, 129.2, 128.4, 128.3, 128.2, 77.6, 61.2, 56.7, 49.7, 40.9, 17.4, 14.0; FTIR (neat) 3031, 2982, 1740, 1610, 1456 $cm^{-1}$; HRMS $(M+H)^+$ calcd for $C_{16}H_{23}N_2O_5S$ 355.1328, found 355.1322.

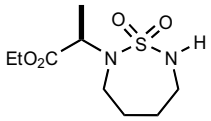
**2,3,4,5,6,7-hexahydro-1,2,7-thiazepine-1,1-dioxo-2,7-diyl-*N*-benzyloxy-*N*'-(2*R*)-methyl ethanoic acid ethyl ester (3.48)**




To a solution of cyclic sulfamide **3.46** (0.42 mmol, 148 mg) in MeOH (10 mL) was added catalytic amounts of 5% Pd/C (~5 mg). After removal of air from the solution by suction, a $H_2$ balloon was inserted and the reaction stirred at rt for 3 days. The crude product was filtered through celite and purified by flash chromatography ($SiO_2$, 7:1 Heptane/EtOAc) to afford 98 mg (66%) of **3.48** and 23 mg (21%) of **3.49** as clear yellow oils.

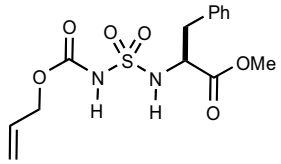
**Analytical data for 3.48:** TLC $R_f$ = 0.55 (1:1 Heptane/EtOAc); $[\alpha]_D^{25}$ = +7.0 (*c* = 0.69, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.35-7.30 (m, 5H), 4.90 (q, *J* = 10.5 Hz, 2H), 4.79 (q, *J* = 7.5 Hz, 1H), 4.10-4.06 (m, 1H), 4.01-3.98 (m, 1H), 3.35-3.30 (m, 1H), 3.27-3.24 (m, 2H), 3.01 (bs, 1H), 2.12 (m, 2H), 1.94-1.90 (m, 1H), 1.76 (m, 1H), 1.40 (d, *J* = 7.5 Hz, 3H), 1.20 (t, *J* = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.7, 135.8, 129.3, 128.3, 128.3, 77.6, 61.0, 57.7, 57.6, 53.9, 41.7, 27.8, 22.4, 14.0; FTIR (neat) 3032, 2939, 1740, 1607, 1497, 1454 $cm^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{16}H_{24}N_2O_5SNa$ 379.1304, found 379.1308.

**2,3,4,5,6,7-hexahydro-1,2,7-thiazepine-1,1-dioxo-2,7-diyl-*N*'-(2*R*)-methyl ethanoic acid ethyl ester (3.49)**




**Analytical data for 3.49:** TLC $R_f$ = 0.23 (1:1 Heptane/EtOAc); $[\alpha]_D^{25}$ = + 2.3 (*c* = 1.08, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) δ 4.82 (t, *J* = 5.0 Hz, 1H), 4.60 (q, *J* = 5.0 Hz, 1H), 4.19 (q, *J* = 10.0 Hz, 2H), 4.31 (ddd, *J* = 15.0, 10.0, 5.0 Hz, 1H), 3.25-3.19 (m, 3H), 1.92-1.86 (m, 2H), 1.85-1.80 (m, 1H), 1.76-1.71 (m, 1H), 1.48 (d, *J* = 5.0 Hz, 3H), 1.28 (t, *J* = 5.0 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 172.3, 61.4, 56.6, 44.6, 42.4, 30.4, 27.4, 16.1, 14.1; FTIR (neat) 3292, 2941, 1734 cm-1; HRMS $(M+H)^+$ calcd for $C_9H_{19}N_2O_4S$ 251.1065, found 251.1060.

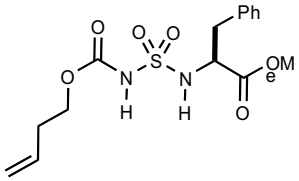
***N*-[[[(2-Propenyloxy)carbonyl]amino]sulfonyl]-(*S*)-phenylalanine methyl ester (4.13)**




To a stirring solution of CSI (1.97 g, 13.9 mmol) in $CH_2Cl_2$, (10 mL) at 0 °C was added allyl alcohol (0.95 mL, 13.9 mmol) via syringe and the reaction was stirred for 1 h. This solution was transferred via cannula to a stirring solution of phenylalanine ester hydrochloride (3.0 g, 13.9 mmol) and $Et_3N$ (3.87 mL, 27.8 mmol) in $CH_2Cl_2$ (25 mL) at 0 °C. The resulting mixture was stirred under Ar for 12 h. The product of the reaction was dissolved in 100 mL of $H_2O$ and extracted with $CH_2Cl_2$ (4 × 50 mL), dried with $Na_2SO_4$, filtered and concentrated under reduced pressure. The product was purified by flash chromatography ($SiO_2$, 3:1 heptane/EtOAc) to afford 2.65 g (56%) of carbamate **4.13** as white solid.

**Analytical data for 4.13:** TLC $R_f$ = 0.38 (1:1 heptane/EtOAc); Mp = 101–102.5 °C; $[\alpha]_D^{25}$ = + 32.9 (*c* = 0.99, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.33-7.27 (m, 3H and N–H), 7.16 (d, *J* = 7.0 Hz, 2H), 5.88 (dddd, *J* = 16.6, 11.3, 5.8, 5.6 Hz, 1H), 5.58 (d, *J* = 8.5 Hz, 1H), 5.34 (d, *J* = 17.1 Hz, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 4.61, (d, *J* = 5.8 Hz, 2H), 4.55-4.51 (m,1H), 3.72, (s, 3H), 3.13 (d, *J* = 5.9 Hz, 2H); $^{13}$C NMR (125 MHz, CDCl3) δ 171.0, 150.6, 134.7, 130.9, 129.4, 128.7, 127.5, 119.5, 67.4, 57.7, 52.7, 39.0; FTIR (neat) 3271, 1740, 1732, 1647 cm$^{-1}$; HRMS $(M+H)^+$ calcd for $C_{14}H_{19}N_2O_6S$ 343.0964, found 343.0957.

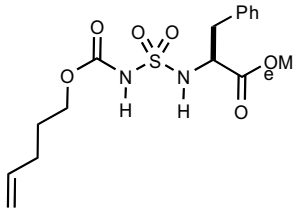
***N*-[[[(2-Butenyloxy)carbonyl]amino]sulfonyl]-(*S*)-phenylalanine methyl ester (4.14)**



In a procedure similar to the preparation of sulfamoyl carbamate **4.13**, CSI (1.21 mL, 13.9 mmol), 3-buten-1-ol (1.2 mL, 13.9 mmol), and (L)-phenylalanine methyl ester hydrochloride (3.0 g, 13.9 mmol) and $Et_3N$ (3.87 mL, 27.8 mmol) were subjected to the aforementioned 3-component coupling conditions. Flash chromatography ($SiO_2$, 2:1 heptane/EtOAc) afforded 3.60 g (73%) of the desired carbamate **4.14** as a white solid.

**Analytical data for 4.14:** TLC $R_f$ = 0.38 (1:1 heptane/EtOAc); Mp = 95-97 °C; $[\alpha]_D^{25}$ = + 38.3 (*c* = 1.05, $CHCl_3$); $^1$H NMR (500 MHz, CDCl3) δ 7.32-7.25 (m, 3H and N–H), 7.15 (d, *J* = 6.8 Hz, 2H), 5.75 (dddd, *J* = 17.0, 10.2, 6.7, 6.7 Hz, 1H), 5.11 (d, *J* = 17.1 Hz, 1H), 5.07 (d, *J* = 10.3 Hz, 1H), 4.51 (t, *J* = 5.8 Hz, 1H), 4.18 (t, *J* = 6.6 Hz, 2H), 3.72 (s, 3H), 3.13 (d, *J* = 5.8 Hz, 2H), 2.39 (dd, *J* = 13.1, 6.5 Hz, 2H); $^{13}$C NMR (125 MHz, CDCl3) δ 171.0, 150.8, 134.7, 133.3, 129.4, 128.8, 127.5, 117.8, 65.9, 57.6, 52.7, 38.8, 32.8; FTIR (neat) 3273, 2955, 1744, 1642 $cm^{-1}$; HRMS $(M+H)^+$ calcd for $C_{15}H_{21}N_2O_6S$ 357.1120, found 357.1099.

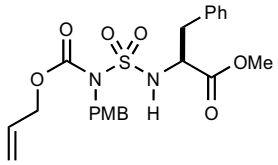
***N*-[[[(2-Pentenyloxy)carbonyl]amino]sulfonyl]-(*S*)-phenylalanine methyl ester (4.15).**




In a procedure similar to the preparation of sulfamoyl carbamate **4.13**, CSI (1.21 mL, 13.9 mmol), 4-penten-1-ol (1.44 mL, 13.9 mmol), (L)-phenyl alanine methyl ester hydrochloride (3.0 g, 13.9 mmol) and $Et_3N$ (3.87 mL, 27.8 mmol) were subjected to 3-component coupling conditions. Flash chromatography ($SiO_2$, 3:1 heptane/EtOAc) afforded 3.17 g (62%) of the desired carbamate **4.15** as white solid.

**Analytical data for 4.15:** TLC $R_f$ = 0.21 (2:1 heptane/EtOAc); Mp = 101–103 °C; $[\alpha]_D^{25}$ = + 35.0 (*c* = 1.03, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.35-–7.25 (m, 3H), 7.16 (d, *J* = 7.1 Hz, 2H), 5.77 (dddd, *J* = 16.9, 10.2, 6.6, 6.6 Hz, 1H), 5.58 (dd, *J* = 12.6, 8.5 Hz, 1H), 5.04 (dd, *J* = 17.2, 1.0 Hz, 1H), 5.00 (dd, *J* = 10.2, 1.1 Hz, 1H), 4.52 (dd, *J* = 14.3, 5.9 Hz, 1H), 4.14 (t, *J* = 6.6 Hz, 2H), 3.72 (s, 3H), 3.13 (d, *J* = 5.9 Hz, 2H), 2.08 (q, *J* = 7.1 Hz, 2H), 1.73 (quintet, *J* = 7.1 Hz, 2H); $^{13}$C NMR (125 MHz, CDCl3) δ 171.0, 150.9, 137.0 134.7, 129.4 128.7, 127.4, 115.7, 66.5, 57.7, 52.7, 39.0, 29.7, 27.6; FTIR (neat) 3271, 1744, 1641 $cm^{-1}$; HRMS $(M+H)^+$ calcd for $C_{16}H_{23}N_2O_6S$ 371.1277, found 371.1280.

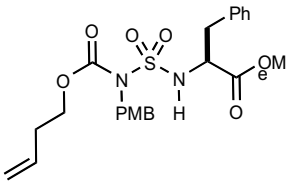
**_N_-[[[(2-Propenyloxy)carbonyl]-N'-(4-methoxybenzyl)-amino]sulfonyl]-(_S_)-phenylalanine methyl ester (4.16)**




To a stirring solution of $Ph_3P$ (1.85 g, 7.04 mmol) in THF (4 mL) at rt was added PMBOH (973 mg, 7.04 mmol) via syringe and the solution stirred for 30 min. This mixture was transferred via cannula to a stirring solution of sulfamoyl carbamate **4.13** (2.41 g, 7.04 mmol) and DIAD (1.42 g, 7.04 mmol) in THF (5 mL) and the reaction was stirred for 3 h and concentrated under reduced pressure. Flash chromatography ($SiO_2$, 4:1 heptane/EtOAc) afforded 3.17 g (97%) of the desired alkylated sulfamoyl carbamate **4.16** as a yellow oil.

**Analytical data for 4.16:** TLC $R_f$ = 0.49 (1:1 heptane/EtOAc); $[\alpha]_D^{25}$ = +2.9 (*c* = 1.02, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.6 Hz, 2H), 7.31–7.28 (m, 3H), 7.07 (d, *J* = 6.3 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.90 (dddd, *J* = 16.6, 11.2, 5.8, 5.4 Hz, 1H), 5.74 (d, *J* = 8.2 Hz, 1H), 5.36 (d, *J* = 17.2 Hz, 1H), 5.28 (d, *J* = 10.4 Hz, 1H), 4.85 (d, *J* = 15.3 Hz, 1H), 4.73 (d, *J* = 15.3 Hz, 1H), 4.71–4.74 (m, 2H), 4.06 (dd, *J* = 14.0, 5.9 Hz, 1H), 3.82 (s, 3H), 3.61 (s, 3H), 3.03 (d, *J* = 9.4 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 170.6, 159.4, 152.6, 136.2, 134.8, 131.0, 130.1, 129.3, 128.6, 127.3, 119.4, 113.9, 67.4, 57.0, 55.2, 52.4, 50.3, 38.9; FTIR (neat) 3304, 2979, 1736, 1728, 1612, 1514 $cm^{-1}$; HRMS $(M+H)^+$ calcd for $C_{22}H_{27}N_2O_7S$ 463.1539, found 463.1566.

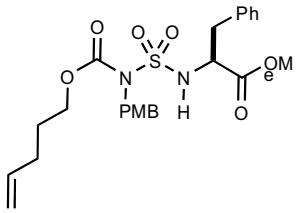
***N*-[[[(2-Butenyloxy)carbonyl]-*N*'-(4-methoxybenzyl)-amino]sulfonyl]-(*S*)-phenylalanine methyl ester (4.17)**




In a procedure similar to the preparation of sulfamoyl carbamate **4.16**, compound **4.14** (3.56 g, 9.99 mmol), DIAD (1.97 mL, 9.99 mmol), $Ph_3P$ (2.62 g, 9.99 mmol) and PMBOH (1.25 mL g, 9.99 mmol) were utilized in the Mitsunobu reaction. Flash chromatography ($SiO_2$, 5:1 heptane/EtOAc) afforded 3.94 g (83%) of the desired alkylated product **4.17** as a yellow oil.

**Analytical data for 4.17:** TLC $R_f$ = 0.55 (1:1 heptane/EtOAc); $[\alpha]_D^{25}$ = + 3.0 (*c* = 1.00, $CHCl_3$); $_1$H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.5 Hz, 2H), 7.27–7.24 (m, 3H), 7.05 (d, *J* = 7.0 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 5.75–5.69 (m, 1H and N–H), 5.10 (d, *J* = 17.2 Hz, 1H), 5.00 (d, *J* = 10.2 Hz, 1H), 4.82 (d, *J* = 15.2 Hz, 1H), 4.68 (d, *J* = 15.2 Hz, 1H), 4.24 (t, *J* = 6.5 Hz, 2H), 4.02 (dd, *J* = 14.2, 5.9 Hz, 1H), 3.80 (s, 3H), 3.59 (s, 3H), 2.98 (d, *J* = 5.9 Hz, 2H), 2.40 (dd, *J* = 12.8, 6.4 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 170.6, 159.3, 152.8, 134.8, 134.0, 130.2, 129.4, 129.2, 128.6, 127.3, 117.8, 113.8, 66.4, 56.9, 55.3, 52.4, 50.2, 39.0, 32.9; FTIR (neat) 3319, 3055, 2926, 1744, 1728, 1612, 1514 $cm^{-1}$; HRMS $(M+NH_4)^+$ calcd for $C_{23}H_{32}N_3O_7S$ 494.1961, found 494.1953.

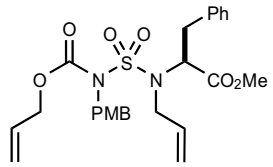
***N*-[[[(2-Pentenyloxy)carbonyl]-*N*'-(4-methoxybenzyl)-amino]sulfonyl]-(*S*)-phenylalanine methyl ester (4.18)**




In a procedure similar to the preparation of sulfamoyl carbamate **4.16**, compound **4.15** (3.0 g, 8.1 mmol), DIAD (1.59 mL, 8.1 mmol), $Ph_3P$ (2.12 g, 8.1 mmol) and PMBOH (1.0 mL, 8.1 mmol) were utilized in the Mitsunobu reaction. Flash chromatography ($SiO_2$, 4:1 heptane/EtOAc) afforded 3.08 g (78%) of the desired alkylated product **4.18** as a yellow oil.

**Analytical data for 4.18:** TLC $R_f$ = 0.54 (1:1 heptane/EtOAc); $[\alpha]_D^{25}$ = + 3.3 (*c* = 1.01, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.6 Hz, 2H), 7.31–7.27 (m, 3H), 7.08 (d, *J* = 6.5 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.78 (dddd, *J* = 16.9, 10.2, 6.6, 6.6 Hz, 1H), 5.73 (d, *J* = 5.5 Hz, 1H), 5.03 (dd, *J* = 16.9, 1.5 Hz, 1H), 5.00 (d, *J* = 9.0 Hz, 1H), 4.85 (d, *J* = 15.3 Hz, 1H), 4.72 (d, *J* = 15.3, 1H), 4.24–4.17 (m, 2H), 4.06 (dd, *J* = 13.9, 5.9 Hz, 1H), 3.82 (s, 3H), 3.62 (s, 3H), 3.01 (d, *J* = 5.8 Hz, 2H), 2.08 (dt, *J* = 7.4, 7.1 Hz, 2H), 1.75 (quintet, *J* = 7.1 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 170.6, 159.3, 152.8, 137.0, 134.8, 129.9, 129.3, 129.1, 128.6, 127.3, 115.6, 113.8, 67.0, 57.0, 55.2, 52.4, 50.2, 38.9, 29.7, 27.6; FTIR (neat) 3296, 1728, 1612, 1514 $cm^{-1}$; HRMS $(M+NH_4)^+$ calcd for $C_{24}H_{34}N_3O_7S$ 508.2117, found 508.2094.

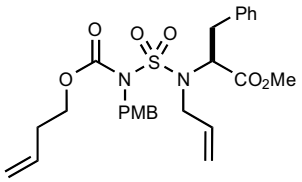
***N*-(2-Propenyl)-*N*-[[[(2-propenyloxy)carbonyl]-*N*'-(4-methoxybenzyl) amino]sulfonyl]-(*S*)-phenylalanine methyl ester (4.19)**




To a stirring solution of **4.16** (3.06 g, 6.62 mmol) in $CH_3CN$ (25 mL) was added $K_2CO_3$ (9.15 g, 66.2 mmol), and allyl bromide (2.86 mL, 33.1 mmol). The reaction was stirred under reflux for 24 h. The product was filtered and purified by flash chromatography ($SiO_2$, 5:1 heptane/EtOAc) to afford 2.01 g (60%) of the pure product **4.19** as a yellow oil.

**Analytical data for 4.19:** TLC $R_f$ = 0.51 (1:1 heptane/EtOAc). $[\alpha]_D^{25}$ = -15.1 (*c* = 1.09,$CHCl_3$); $^1$H NMR (400 MHz, CDCl3) δ 7.37 (d, *J* = 8.6 Hz, 2H), 7.30–7.21 (m, 3H), 7.12 (d, *J* = 6.9 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 5.97–5.85 (m, 2H), 5.35 (d, *J* = 17.1 Hz, 1H), 5.28 (d, *J* = 10.4 Hz, 1H), 5.25 (d, *J* = 17.6 Hz, 1H), 5.17 (d, *J* = 10.2 Hz, 1H), 4.87 (d, *J* = 15.4 Hz, 1H), 4.77 (d, *J* = 15.4 Hz, 1H), 4.65 (d, *J* = 5.9 Hz, 2H), 4.55 (dd, *J* = 8.9, 6.2 Hz, 1H), 4.17 (dd, *J* = 16.7, 5.7 Hz, 1H), 4.00 (dd, *J* = 16.7, 6.8 Hz, 1H), 3.77 (s, 3H), 3.59 (s, 3H), 3.22 (dd, *J* = 13.7, 9.0 Hz, 1H), 2.97 (dd, *J* = 13.7, 6.2 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.3, 159.1, 152.5, 136.2, 134.9, 131.2, 129.9, 129.1, 129.0, 128.4, 126.8, 119.4, 117.6, 113.6, 67.7, 61.1, 55.1, 52.0, 51.4, 50.0, 36.8; FTIR (neat) 3350, 2982, 1732, 1649, 1612, 1585, 1514 $cm^{-1}$; HRMS $(M+H)^+$ calcd for $C_{25}H_{31}N_2O_7S$ 503.1852, found 503.1863.

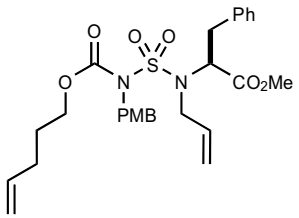
***N*-(2-Propenyl)-*N*-[[[(2-butenyloxy)carbonyl]-*N*'-(4-methoxybenzyl)amino]-sulfonyl]-(*S*)-phenylalanine methyl ester (4.20)**




In a procedure similar to the preparation of sulfamoyl carbamate **4.19**, **4.17** (1.58 g, 3.3 mmol), $K_2CO_3$ (912 mg, 6.6 mmol), and allyl bromide (0.29 mL, 3.30 mmol) was subjected to the allylation procedure. Flash chromatography ($SiO_2$, 100% EtOAc) afforded 1.68 g (98%) of **4.20** as a yellow oil.

**Analytical data for 4.20:** TLC $R_f$ = 0.60 (1:1 heptane/EtOAc); $[\alpha]_D^{25}$ = -19.8 (*c* = 0.98, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.6 Hz, 2H), 7.29–7.22 (m, 3H), 7.13 d, *J* = 7.0 Hz, 2H), 6.81 (d, *J* = 11.5 Hz, 2H), 5.91 (dddd, *J* = 16.9, 10.2, 6.3, 6.1 Hz, 1H), 5.75 (dddd, *J* = 17.0, 10.3, 6.7, 6.7 Hz, 1H), 5.25 (dd, *J* = 17.2, 1.1 Hz, 1H), 5.16 (dd, *J* = 10.3, 1.0 Hz, 1H), 5.12 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.10 (dd, *J* = 9.3, 1.3 Hz, 1H), 4.83 (d, *J* = 15.5 Hz, 1H), 4.74 (d, *J* = 15.5 Hz, 1H), 4.58 (dd, *J* = 8.9, 6.2 Hz, 1H), 4.20 (t, *J* = 6.3 Hz, 2H), 4.17 (d, *J* = 5.7 Hz, 1H)), 4.02 (dd, *J* = 16.6, 6.7 Hz, 1H), 3.77 (s, 3H), 3.59 (s, 3H), 3.22 (dd, *J* = 13.7, 9.0 Hz, 1H), 2.97 (dd, *J* = 13.7, 6.1 Hz, 1H), 2.42 (dd, *J* = 13.5, 6.7 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 170.4, 159.3, 152.7, 136.3, 135.0, 133.3, 129.9, 129.2, 129.1, 128.4, 126.8, 117.8, 117.7, 113.7, 66.3, 61.2, 55.2, 52.0, 51.4, 49.9, 36.9, 33.0; FTIR (neat) 2955, 1728, 1612, 1514 $cm^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{26}H_{32}N_2O_7SNa$ 539.1828, found 539.1834.

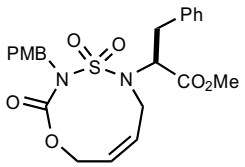
***N*-(2-Propenyl)-*N*-[[[(2-pentenyloxy)carbonyl]-*N*'-(4-methoxybenzyl)amino]-sulfonyl]-(*S*)-phenylalanine methyl ester (4.21)**




In a procedure similar to the preparation of sulfamoyl carbamate **4.19**, **4.18** (513 mg, 3.3 mmol), $K_2CO_3$ (1.45 g, 10.5 mmol), allyl bromide (0.45 mL, 5.23 mmol) in $CH_3CN$ (20 mL) was subjected to the allylation procedure. Flash chromatography ($SiO_2$, 4:1 heptane/EtOAc) afforded 506 mg (91%) of **4.21** as a yellow oil.

**Analytical data for 4.21:** TLC $R_f$ = 0.67 (1:1 heptane/EtOAc); $[\alpha]_D^{25}$ = -20.2 (*c* = 0.92, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) d 7.38 (d, *J* = 8.7 Hz, 2H), 7.33–7.25 (m, 3H), 7.17 (d, *J* = 6.8 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.95 (dddd, *J* = 16.9, 10.2, 6.5, 5.9 Hz. 1H), 5.80 (dddd, *J* = 16.9, 10.2, 6.6, 6.6 Hz, 1H), 5.29 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.20 (dd, *J* = 10.2, 1.1 Hz, 1H), 5.05 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.04 (d, *J* = 10.0, 1.5 Hz, 1H), 4.89 (d, *J* = 15.5 Hz, 1H), 4.79 (d, *J* = 15.5 Hz, 1H), 4.61 (dd, *J* = 8.9, 6.2 Hz, 1H), 4.22 (dd, *J* = 16.3, 5.7 Hz, 1H), 4.19 (t, *J* = 7.0 Hz, 2H), 4.07 (dd, *J* = 16.6, 6.7 Hz, 1H), 3.80 (s, 3H), 3.63 (s, 3H), 3.26 (dd, *J* = 13.7, 8.9 Hz, 1H), 3.01 (dd, *J* = 13.7, 6.2 Hz, 1H), 2.11 (q, *J* = 7.1 Hz, 2H), 1.79 (quintet, *J* = 7.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.3, 159.1, 152.7, 136.9, 136.2, 134.9, 129.6, 129.1, 129.0, 128.3, 126.8, 117.6, 115.5, 113.6, 66.5, 61.1, 55.1, 52.0, 51.4, 49.9, 36.8, 29.6, 27.6; FTIR (neat) 1728, 1612, 1514 $cm^{-1}$; HRMS $(M+NH_4)^+$ calcd for $C_{27}H_{38}N_3O_7S$ 548.2430, found 540.2431.

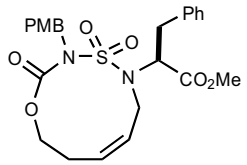
**(2*S*)-2-[3-(4-Methoxy)benzyl)-2,4,4-trioxo-3,4,6,9-tetrahydro-2H-4λ$^6$ [1,4,3,5]-oxathiadiazonin-5-yl]-3-phenyl-propionic acid methyl ester (4.22)**




Compound **4.19** (202 mg, 0.40 mmol) was dissolved in DCE (80 mL, 0.005M) and the solution was degassed with Ar for 15 min followed by reflux for 30 min. Cat-C (75 mg, 22 mol%) was added to the refluxing solution in three equal portions over a period of 48 h. The reaction was cooled to rt, DCE was removed under reduced pressure, followed the addition of DMSO (0.32 mL, 50 equiv relative to catalyst) in $CH_2Cl_2$ (50 mL). The reaction was stirred at rt for 24 h and the solvent was removed under reduced pressure. Flash chromatography ($SiO_2$, 4:1 heptane/EtOAc) afforded 124 mg (65%) of **4.22** as a yellow oil.

**Analytical data for 4.22:** TLC $R_f$ = 0.47 (1:1 heptane/EtOAc); $[\alpha]_D^{25}$ = -60.6 (*c* = 1.11, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.9 Hz, 2H), 7.30 (d, *J* = 7.4 Hz, 2H), 7.24-7.22 (m, 3H), 6.81 (d, *J* = 8.7 Hz, 2H), 5.74 (dd, *J* = 11.5 Hz, 1.7 Hz, 1H), 5.59 (dd, *J* = 9.2, 1.8 Hz, 1H), 5.24–5.14 (m, 1H), 4.83 (s, 2H), 4.71–4.67 (m, 1H), 4.61 (t, *J* = 7.3 Hz, 1H), 3.80–3.75 (m, 1H), 3.75 (s, 3H), 3.53 (s, 3H), 3.41 (dd, *J* = 14.4, 7.6 Hz, 1H), 2.98 (dd, *J* = 14.4, 7.6 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 170.8, 159.2, 153.1, 136.1, 132.0, 130.1, 129.0, 128.8, 128.6, 127.0, 124.5, 113.7, 64.9, 59.4, 55.2, 52.5, 50.7, 43.6, 34.8; FTIR (neat) 2950, 1740, 1612, 1514 cm$^{-1}$; HRMS $(M+NH_4)^+$ calcd for $C_{23}H_{29}N_3O_7S$ 492.1804, found 492.1793.

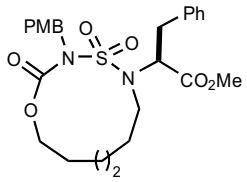
**(2*S*)-2-[3-(4-Methoxybenzyl)-2,4,4-trioxo-3,4,9,10tetrahydro-2*H*,6*H*-4λ$^6$-[1,4,3,5] oxathiadiazonin-5-yl]-3-phenyl-propionic acid methyl ester (4.23)**




In a procedure similar to the preparation of cyclic sulfamoyl carbamate **4.22**, **4.20** (209 mg, 0.40 mmol) and cat-C (34 mg, 10 mol%) in DCE (80 mL) was subjected to the RCM procedure. Flash chromatography ($SiO_2$, 4:1 heptane/EtOAc) afforded 173 mg (87%) of **4.23** as an ivory-colored solid.

**Analytical data for 4.23:** Mp = 43-50 °C; TLC $R_f$ = 0.16 (2:1 heptane/EtOAc); $[\alpha]_D^{25}$ = - 97.5 (*c* = 0.96, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.6 Hz, 2H), 7.31 (d, *J* = 7.2 Hz, 2H), 7.27–7.24 (m, 3H). 6.78 (d, *J* = 8.6 Hz, 2H), 5.85 (ddd, *J* = 10.8, 8.2, 8.0 Hz, 1H), 5.62 (ddd, *J* = 11.0, 11.0, 5.5 Hz, 1H), 4.82 (d, *J* = 15.1 Hz, 1H), 4.76 (d, *J* = 15.1 Hz, 1H), 4.59 (bs,1H), 4.52 (t, *J* = 7.4 Hz, 1H), 4.18-4.14 (m, 1H), 4.08 (dd, *J* = 11.3, 1.1 Hz, 1H), 3.74 (s, 4H), 3.52 (s, 3H), 3.45 (dd, *J* = 14.4, 7.0 Hz, 1H), 3.00 (dd, *J* = 14.4, 7.8 Hz, 1H), 2.74-2.68 (m, 1H), 2.25-2.21 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.3, 159.2, 152.5, 136.5, 131.5, 130.3, 129.1, 129.1, 128.5, 126.9, 113.5, 65.6, 59.2, 55.2, 52.5, 50.8, 44.7, 35.0, 25.3; FTIR (neat) 1732, 1612, 1514 cm$^{-1}$; HRMS $(M+NH_4)^+$ calcd for $C_{24}H_{32}N_3O_7S$ 506.1961, found 506.1955.

**(2*S*)-2-[3-(4-Methoxybenzyl)-2,4,4-trioxo-1-oxa-4λ$^6$-thia-3,5-diaza-cycloundec-7-en-5-yl]-3-phenyl-propionic acid methyl ester (4.24) (hydrogenated for characterization).**



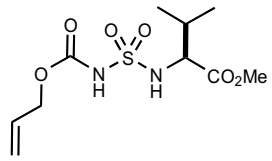

In a procedure similar to the preparation of cyclic sulfamoyl carbamate **4.22**, **4.21** (206 mg, 0.39 mmol) and cat-C (43 mg, 0.05 mmol) in DCE (78 mL) was subjected to the RCM procedure. Flash chromatography ($SiO_2$, 5:1 heptane/EtOAc) afforded 170 mg (87%) of **4.24** (1.6:1 *E*:*Z*) as a yellow oil.

**Analytical data for 4.24:** TLC $R_f$ = 0.50 (1:1 heptane/EtOAc); HRMS $(M+NH_4)^+$ calcd for $C_{25}H_{34}N_3O_7S$ 520.2117, found 520.2091. A portion of this compound was immediately subjected to the following hydrogenation protocol: Cyclic sulfamoyl carbamate **4.24** (57 mg, 0.11 mmol) was weighed into a round-bottomed flask followed by the addition of 5% Pd/C (29 mg) and EtOAc (10 mL). The flask was evacuated using suction followed by the insertion of two $H_2$ balloons. The reaction was stirred at rt for 2 h. The crude product was filtered through celite and concentrated under reduced pressure to afford 54 mg (95%) of a white solid.

**Analytical data for the hydrogenated product:** TLC $R_f$ = 0.49 (1:1 heptanes/EtOAc); Mp = 99-102 °C; $[\alpha]_D^{25}$ = -9.7 (*c* = 0.82, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.5 Hz, 2H), 7.24-7.17 (m, 3H), 6.91 (d, *J* = 6.0 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 5.03 (d, *J* = 15.0 Hz, 1H), 4.81 (d, *J* = 15.0 Hz, 1H), 4.22 (m, 1H), 4.10 (t, *J* = 10.1 Hz, 1H), 3.90 (dd, *J* = 9.8, 3.7 Hz, 1H), 3.73 (s, 3H), 3.68-3.51 (m, 2H), 3.58 (s, 3H), 3.17 (t, *J* = 10.5 Hz, 1H), 2.87 (dd, *J* = 13.3, 4.2 Hz, 1H), 2.05-

1.92 (m, 2H), 1.78–1.66 (m, 2H), 1.56-1.51 (m, 2H), 1.32-1.28 (m, 2H); $^{13}C$ (100 MHz, $CDCl_3$) δ 169.9, 159.2, 152.9, 136.0, 130.5, 129.1, 129.0, 128.4, 126.7, 113.6, 69.2, 60.6, 55.1, 52.0, 51.5, 46.9, 34.9, 25.8, 23.4, 23.3, 22.1; FTIR (neat) 2953, 1743, 1726, 1612, 1514 $cm^{-1}$; HRMS $(M+Na)^+$ calcd for $C_{25}H_{32}N_2O_7SNa$ 527.1828, found 527.1820.

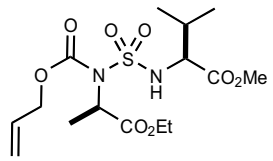
***N*-[[[(2-Propenyloxy)carbonyl]amino]sulfonyl]-(*S*)-valine methyl ester (4.25)**




To a solution of CSI (4.2 g, 29.8 mmol) in $CH_2Cl_2$ (10 mL) at 0 °C was added allyl alcohol (1.73 g, 29.8 mmol) via syringe. In an adjacent round-bottomed flask, valine methyl ester hydrochloride (5.0 g, 29.8 mmol) was dissolved in $CH_2Cl_2$ (25 mL), cooled to 0 °C, and $Et_3N$ (6.03 g, 59.6 mmol) was added via syringe. Each solution was stirred at 0 °C under Ar for approximately 1h. The CSI/alcohol solution was cannulated into the amino acid solution and the reaction was stirred for 12 h under Ar at 0 °C while slowly warming to rt. The crude product was dissolved in $H_2O$ (100 mL) and extracted with $CH_2Cl_2$ (4 × 50 mL), dried over $Na_2SO_4$, filtered, and concentrated under reduced pressure. Flash chromatography ($SiO_2$, 4:1 heptane/EtOAc) afforded 6.12 g (70%) of the desired carbamate **4.25** as white solid.

**Analytical data for 4.25:** TLC $R_f$ = 0.35 (1:1 heptane/EtOAc); Mp = 93-95 °C; $[\alpha]_D^{25}$ = +43.6 (*c* = 1.03, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.92 (dddd, *J* = 17.0, 10.4, 5.8, 5.8 Hz, 1H), 5.67 (d, *J* = 9.4 Hz, 1H), 5.37 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.29 (dd, *J* = 10.4, 1.1 Hz, 1H), 4.66-4.63 (m, 2H), 4.07 (dd, *J* = 9.4, 5.0 Hz, 1H), 3.75 (s, 3H), 2.20-2.11 (m, 1H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.6, 150.7, 131.0, 119.4, 67.3, 62.2, 52.5, 31.4, 18.8, 17.2; FTIR (neat) 3276, 3205, 2966, 1744, 1720, 1651 $cm^{-1}$; HRMS $(M+H)^+$ calcd for $C_{10}H_{19}N_2O_6S$ 295.0964, found 295.0947.

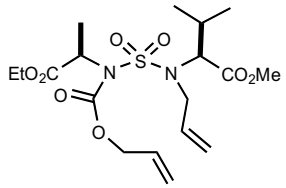
***N*-[[[[*N*'-(2-Propenyloxy)carbonyl]-*N*'-(1*R*)-1-ethoxycarbonyl ethyl]amino]-sulfonyl]-(*S*)-valine methyl ester (4.26)**




Compound **4.25** (2.66 g, 9.0 mmol) was dissolved in THF (3 mL) followed by the addition of DIAD (1.82 g, 9.0 mmol) dropwise via syringe. In an adjacent round bottomed flask, $Ph_3P$ (2.37 g, 9.0 mmol) was dissolved in THF (4 mL) followed by the addition of (*S*)-ethyl lactate (1.02 mL, 9.0 mmol) via syringe. Each solution was stirred under Ar atmosphere at rt for 1 h after which the $Ph_3P$/ethyl lactate solution was cannulated into the solution of **4.25**/DIAD and the resulting reaction mixture stirred under Ar at rt for 24 h. The reaction was concentrated under reduced pressure. Flash chromatography ($SiO_2$, 9:1 heptane/EtOAc) afforded 2.30 g (65%) of the desired alkylated product **4.26** as a yellow oil.

**Analytical data for 4.26**: TLC $R_f$ = 0.53 (1:1 heptane/EtOAc); $[\alpha]_D^{25}$ = +73.0 (*c* = 1.18, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 6.08 (d, *J* = 7.4 Hz, 1H), 5.95 (dddd, *J* = 16.6, 11.1, 5.7, 5.4 Hz, 1H), 5.39 (d, *J* = 17.2 Hz, 1H), 5.30 (d, *J* = 10.5 Hz, 1H), 4.96 (q, *J* = 7.0 Hz, 1H), 4.71 (t, *J* = 5.6 Hz, 2H), 4.23-4.17 (m, 2H), 4.12 (dd, *J* = 7.0, 3.5 Hz, 1H), 3.77 (s, 3H), 2.22-2.15 (m, 1H), 1.59 (d, *J* = 7.0 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.4, 170.0, 151.7, 131.0, 119.3, 68.1, 61.9, 61.8, 56.6, 52.5, 31.9, 18.8, 17.0, 16.5, 14.1; FTIR (neat) 3304, 2966, 1740, 1726, 1649 cm$^{-1}$; HRMS $(M+H)^+$ calcd for $C_{15}H_{27}N_2O_8S$ 395.1488, found 395.1472.

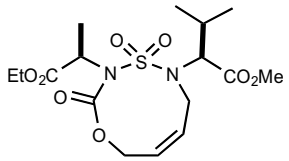
***N*-(2-Propenyl)-*N*-[[[[*N*'-(2-propenyloxy)carbonyl]-*N*'-(1*R*)-1-ethoxycarbonyl-ethyl]amino]sulfonyl]-(*S*)-valine methyl ester (4.27)**




Compound **4.26** (1.10 g, 2.79 mmol) was weighed into a round-bottomed flask, followed by the addition of $K_2CO_3$ (771 mg, 5.58 mmol), allyl bromide (0.24 mL, 2.79 mmol) and $CH_3CN$ (25 mL). The reaction was stirred under reflux at 85 °C for 6 h. The product was filtered and concentrated under reduced pressure. Flash chromatography ($SiO_2$, 6:1 heptane/EtOAc) afforded 825 mg (68%) of diene **4.27** as a yellow oil.

**Analytical data for 4.27:** TLC $R_f$ = 0.38 (2:1 heptane/EtOAc); $[\alpha]_D^{25}$ = -22.2 (*c* = 1.05, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$) δ 6.02 (dddd, *J* = 17.3, 10.2, 5.8, 5.8 Hz, 1H), 5.90 (dddd, *J* = 16.4, 10.6, 5.8, 5.8 Hz, 1H), 5.36 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.29 (dd, *J* = 10.2, 1.0 Hz, 1H), 5.22 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.12 (dd, *J* = 10.2, 1.1 Hz, 1H), 4.99 (q, *J* = 7.0 Hz, 1H), 4.64 (d, *J* = 5.8 Hz, 2H), 4.23-4.21 (m, 2H), 4.19 (d, *J* = 7.1 Hz, 2H), 4.13 (d, *J* = 10.3 Hz, 1H), 3.70 (s, 3H), 2.22-2.14 (m, 1H), 1.61 (d, *J* = 7.0 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 171.0, 170.0, 151.9, 135.3, 131.0, 119.6, 117.5, 67.9, 66.2, 61.7, 56.8, 51.7, 49.5, 28.9, 19.7, 19.4, 16.1, 14.0; FTIR (neat) 2968, 1742, 1647 cm$^{-1}$; HRMS $(M+H)^+$ calcd for $C_{18}H_{31}N_2O_8S$ 435.1801, found 435.1778.

**(2*S*)-2-((1*R*)-1-Ethoxycarbonyl-ethyl])-2,4,4-trioxo-3,4,6,9-tetrahydro-2H-4λ$^6$-[1,4,3,5]oxathiadiazonin-5-yl)-3-methyl-butyric acid methyl ester (4.28)**

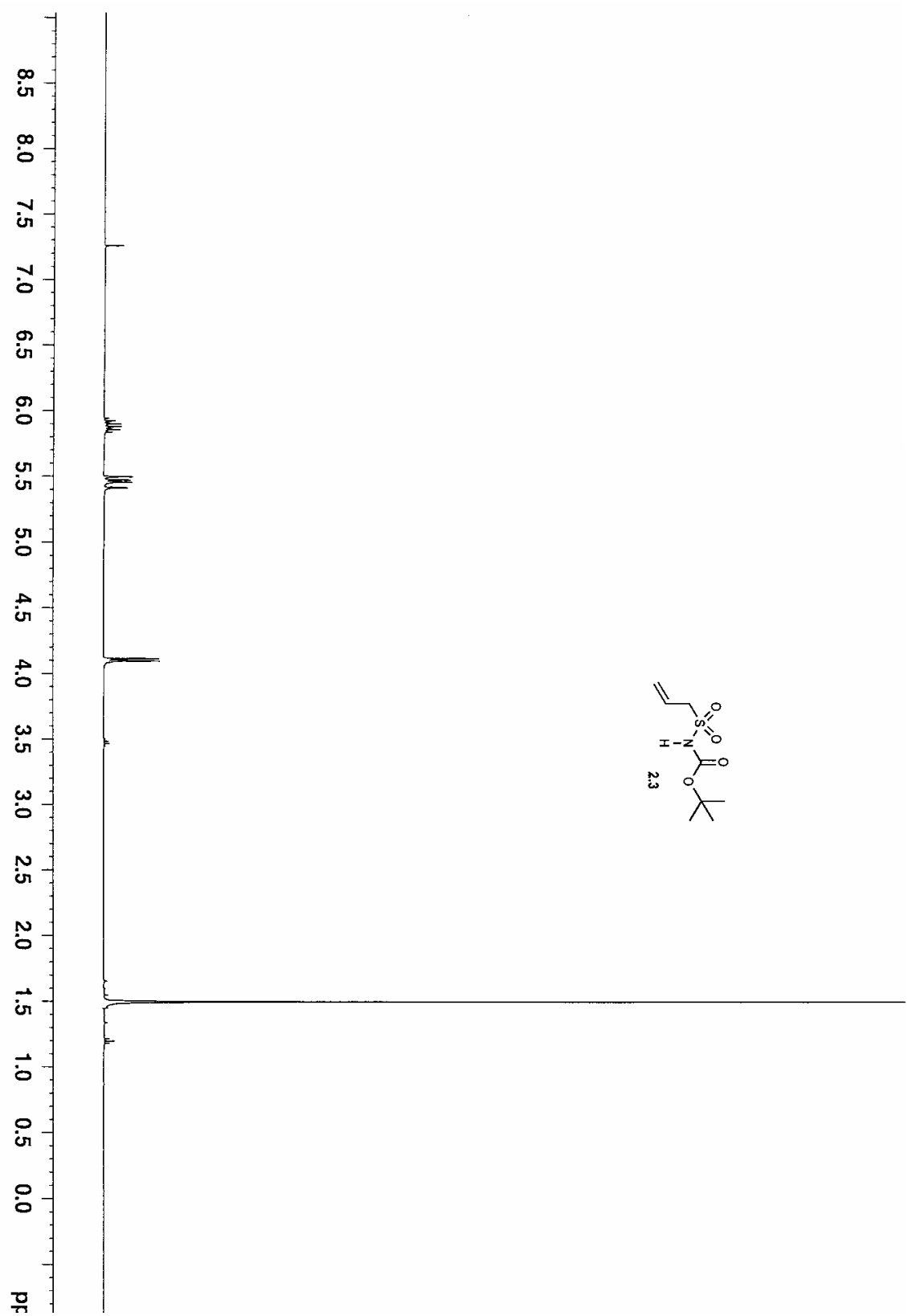



In a procedure similar to the preparation of cyclic sulfamoyl carbamate **4.22**, diene **4.27** (24 mg, 0.055 mmol) and cat-C (4 mg, 8 mol%) in DCE (11 mL) was subjected to the RCM procedure. Flash chromatography ($SiO_2$, 9:1 heptane/EtOAc) afforded 15 mg (68%) of **4.28** as a yellow oil.

**Analytical data for 4.28:** TLC $R_f$ = 0.45 (1:1 heptane/EtOAc); $[\alpha]_D^{25}$ = -77.9 (*c* = 1.00, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.72-5.69 (m, 1H), 5.54-5.51 (m, 1H), 5.33-5.29 (m, 1H), 4.95 (q, *J* = 7.0 Hz, 1H), 4.89-4.85 (m, 1H), 4.73-4.69 (m, 1H), 4.33-4.18 (m, 2H), 3.96 (d, *J* = 10.9 Hz, 1H), 3.57 (s, 3H), 3.57 (m, 1H), 2.37-2.27 (m, 1H), 1.62 (d, *J* = 7.0 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.04 (d, *J* = 6.3 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 170.7, 169.7, 152.6, 130.9, 124.6, 65.3, 61.8, 56.0, 51.8, 43.2, 29.7, 25.9, 20.5, 18.6, 15.6, 14.0; FTIR (neat) 2970, 1744, 1647, 1450, 1386 cm$^{-1}$; HRMS $(M+H)^+$ calcd for $C_{16}H_{27}N_2O_8S$ 407.1488, found 407.1497.

**Apendix**

*Selected NMR's and Crystallographic Data*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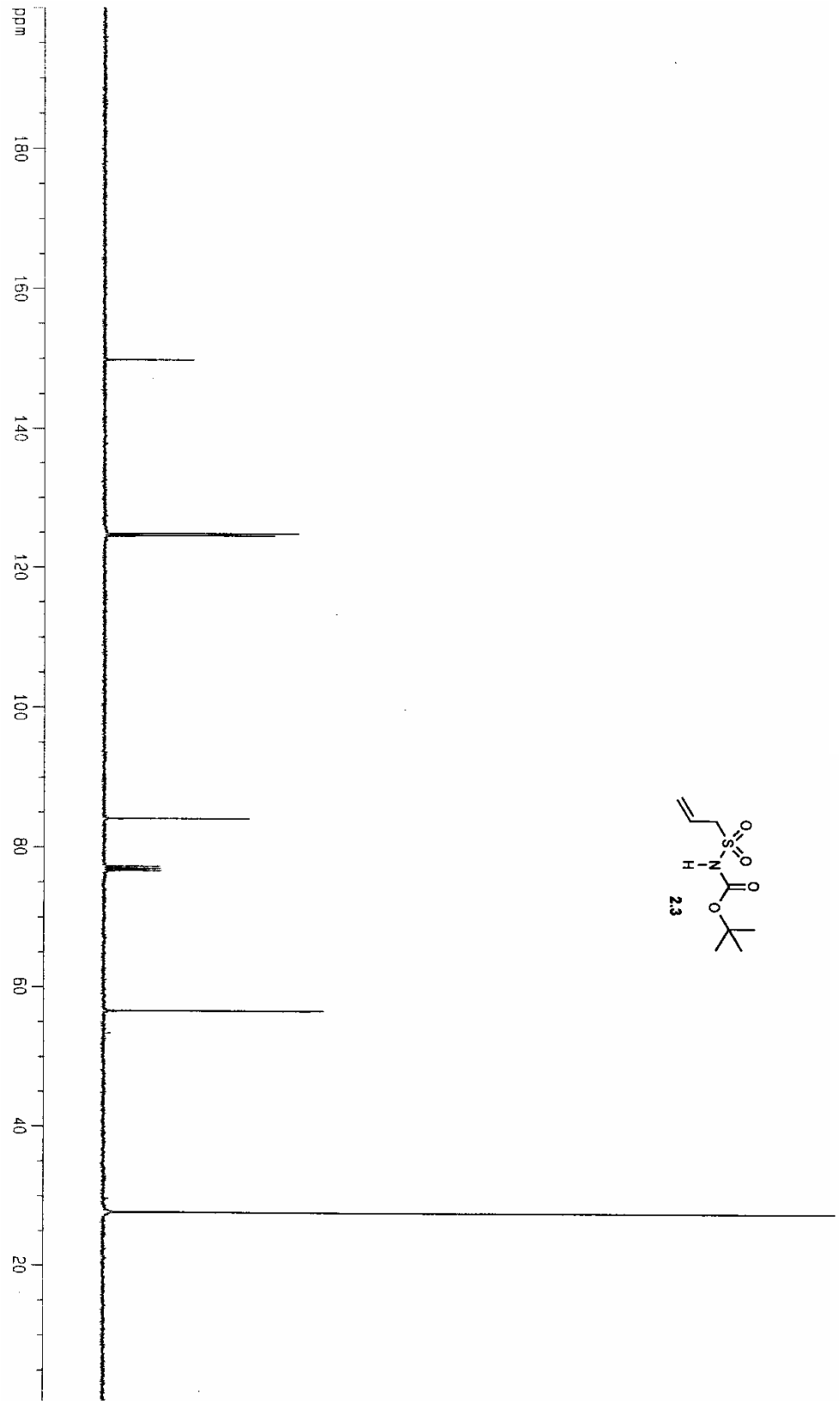
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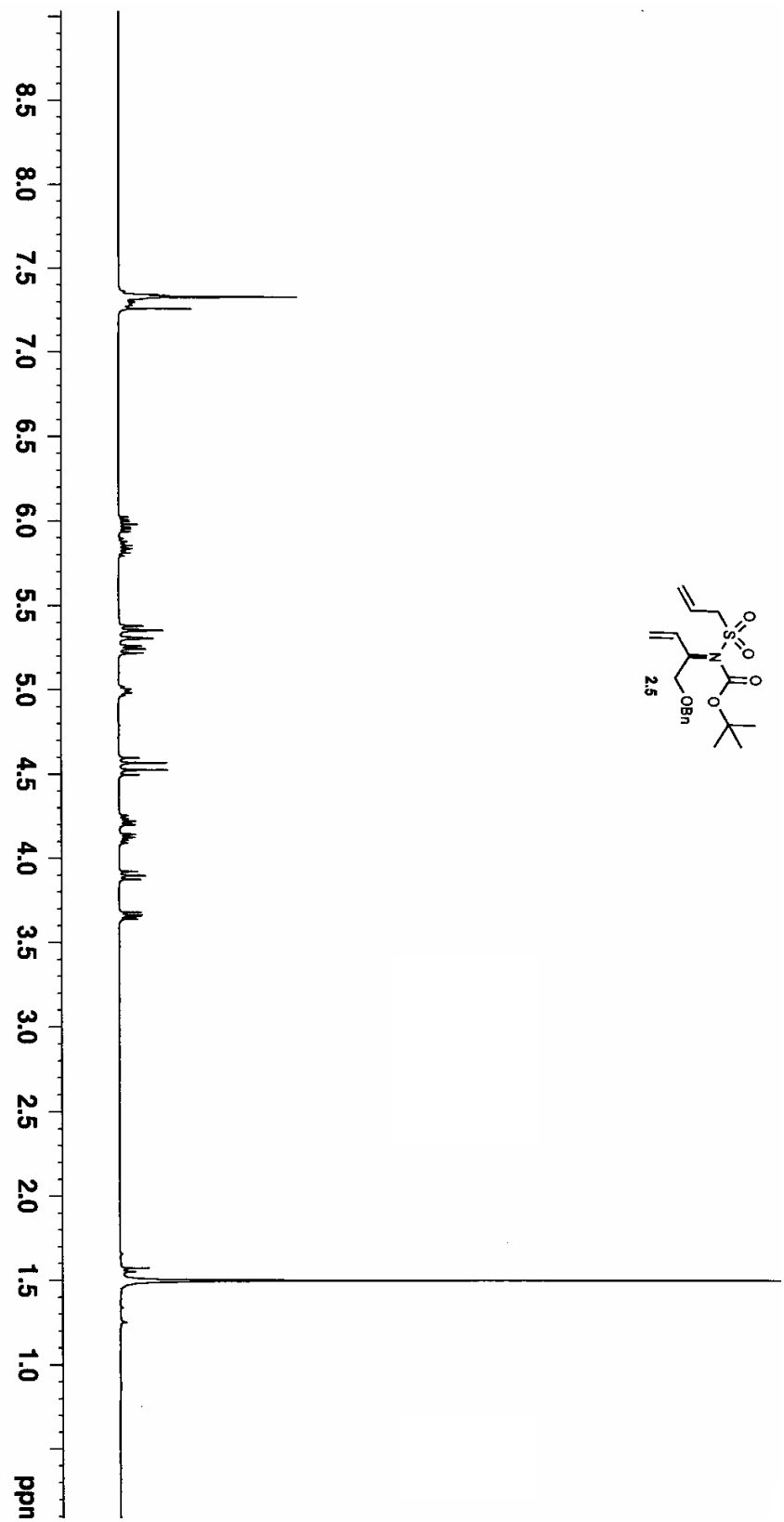
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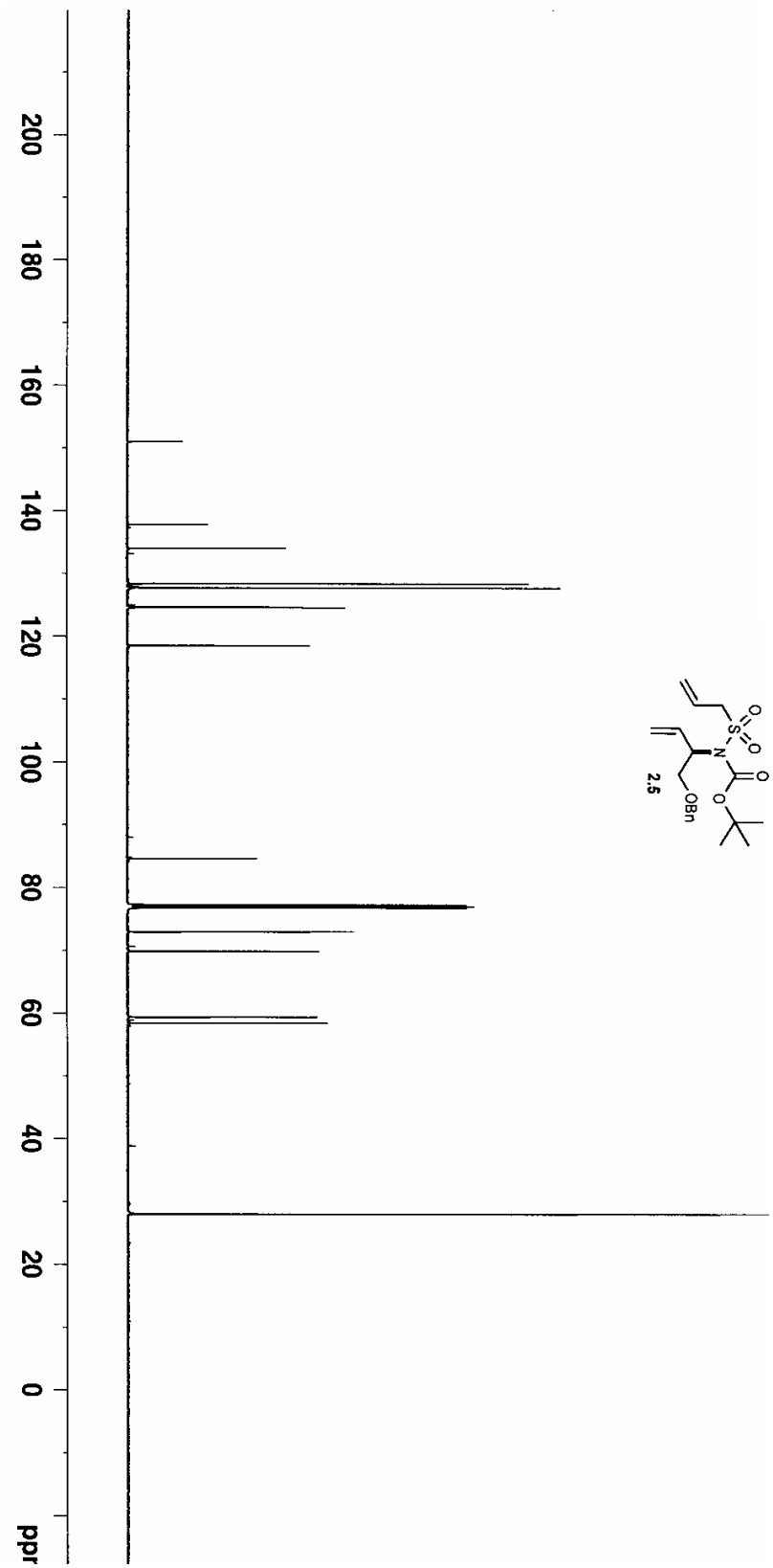
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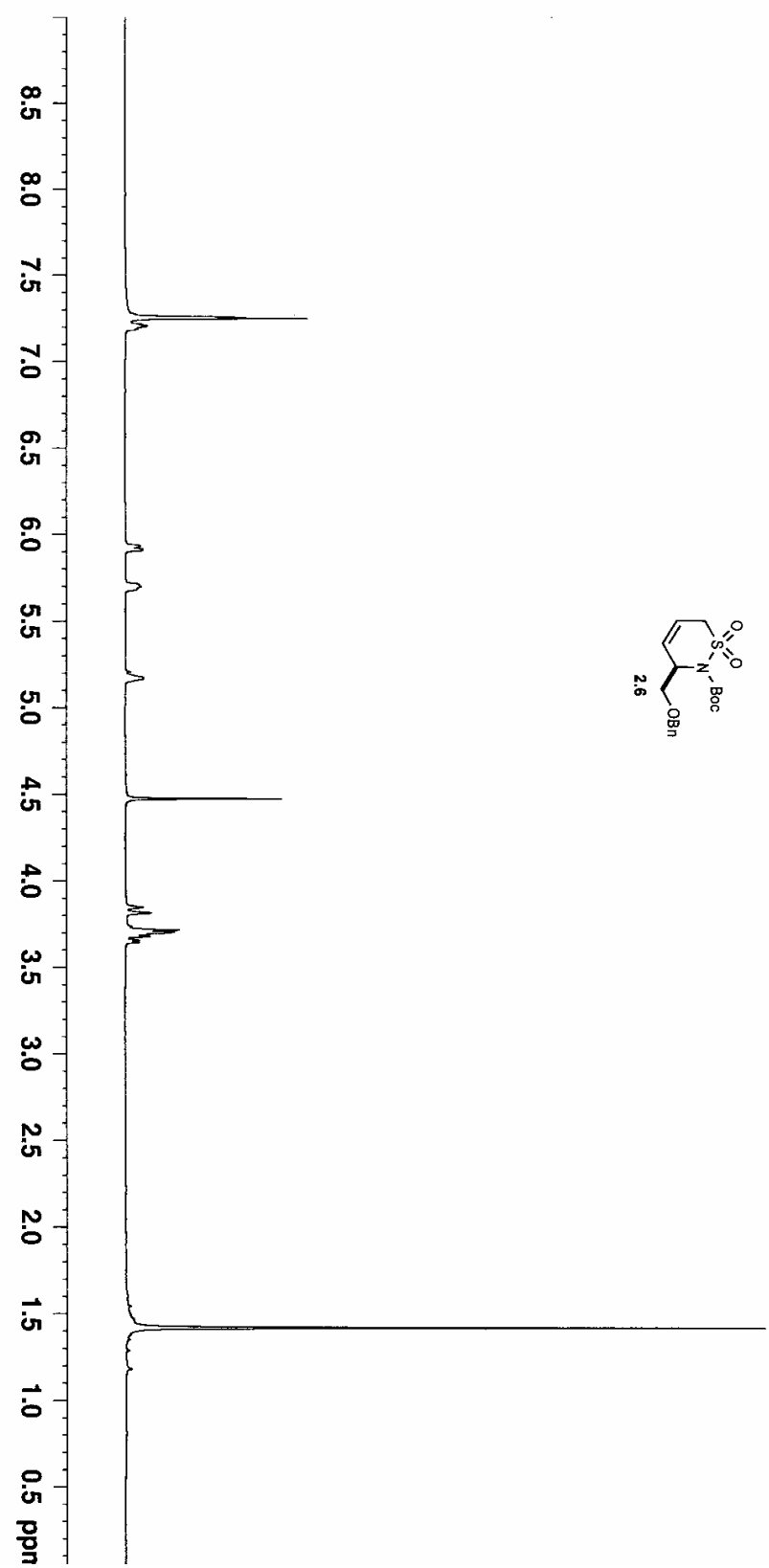
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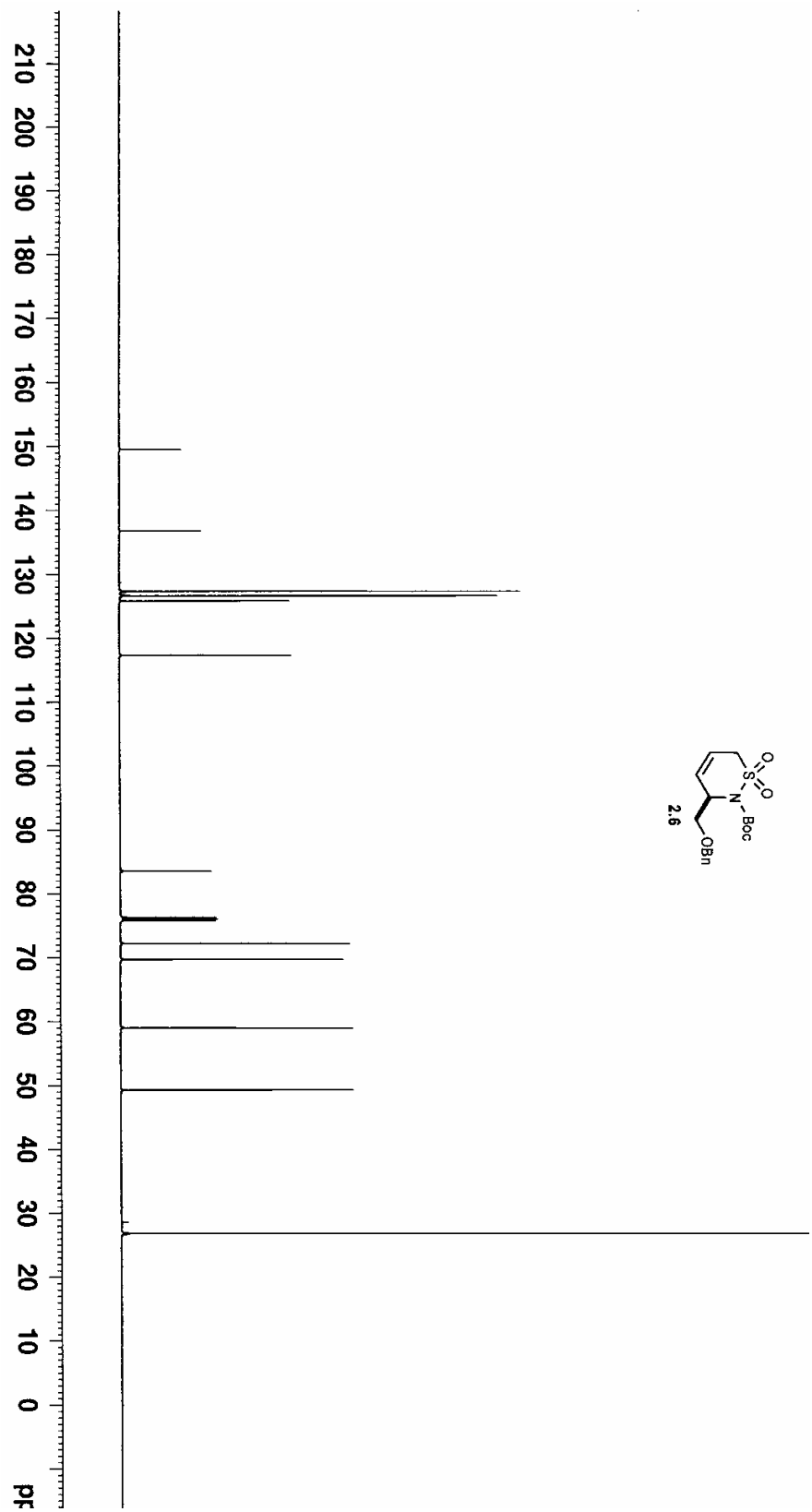
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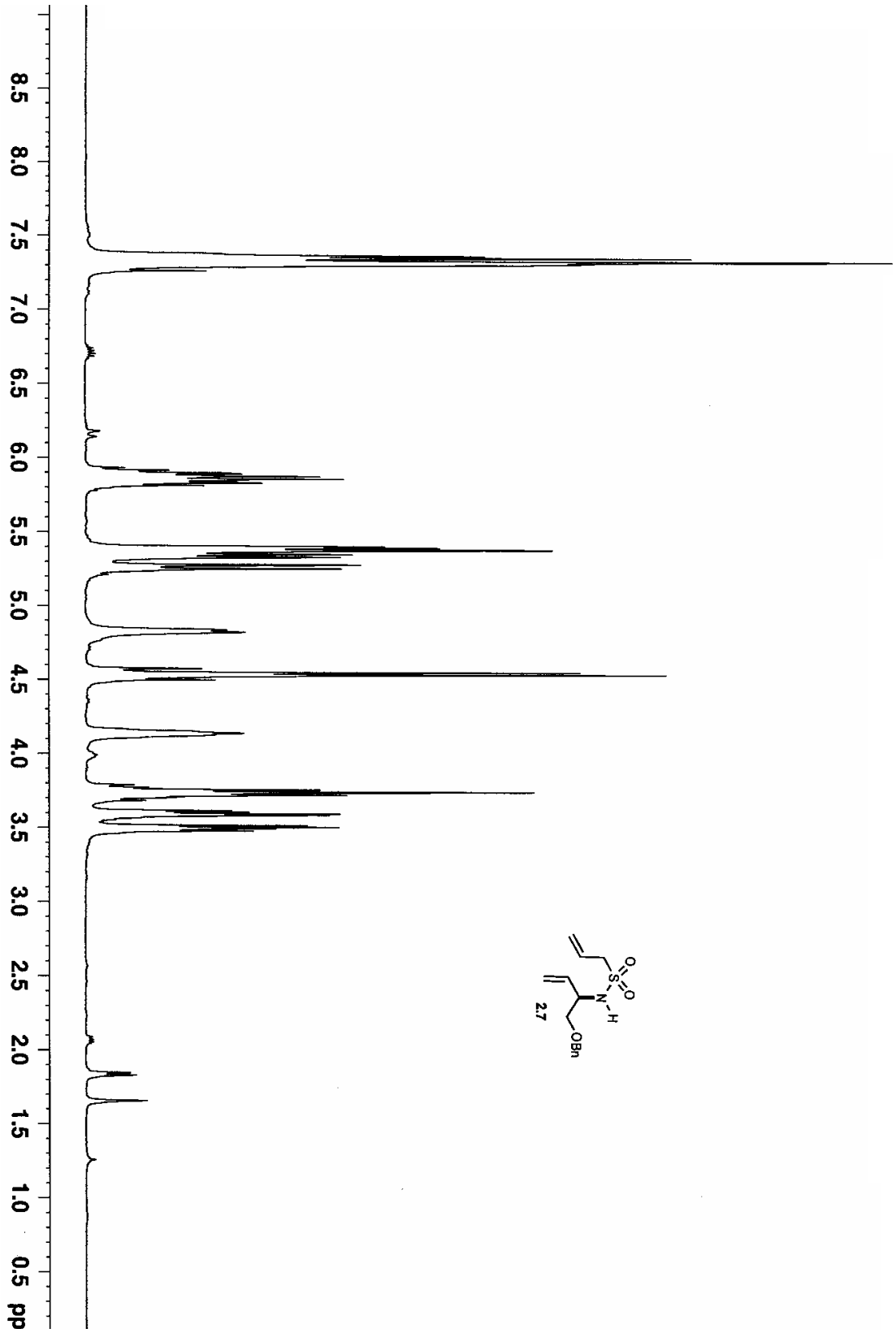
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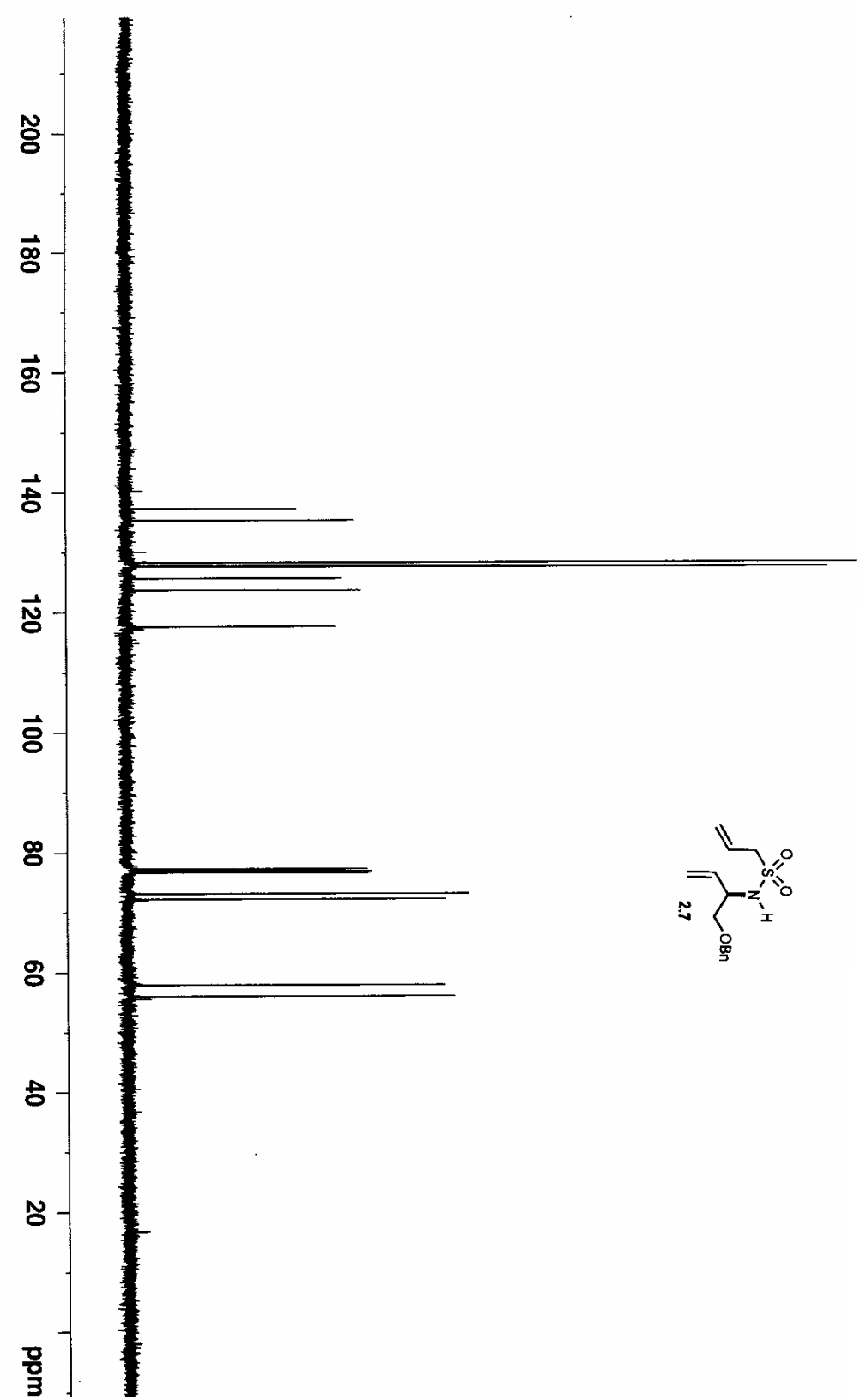
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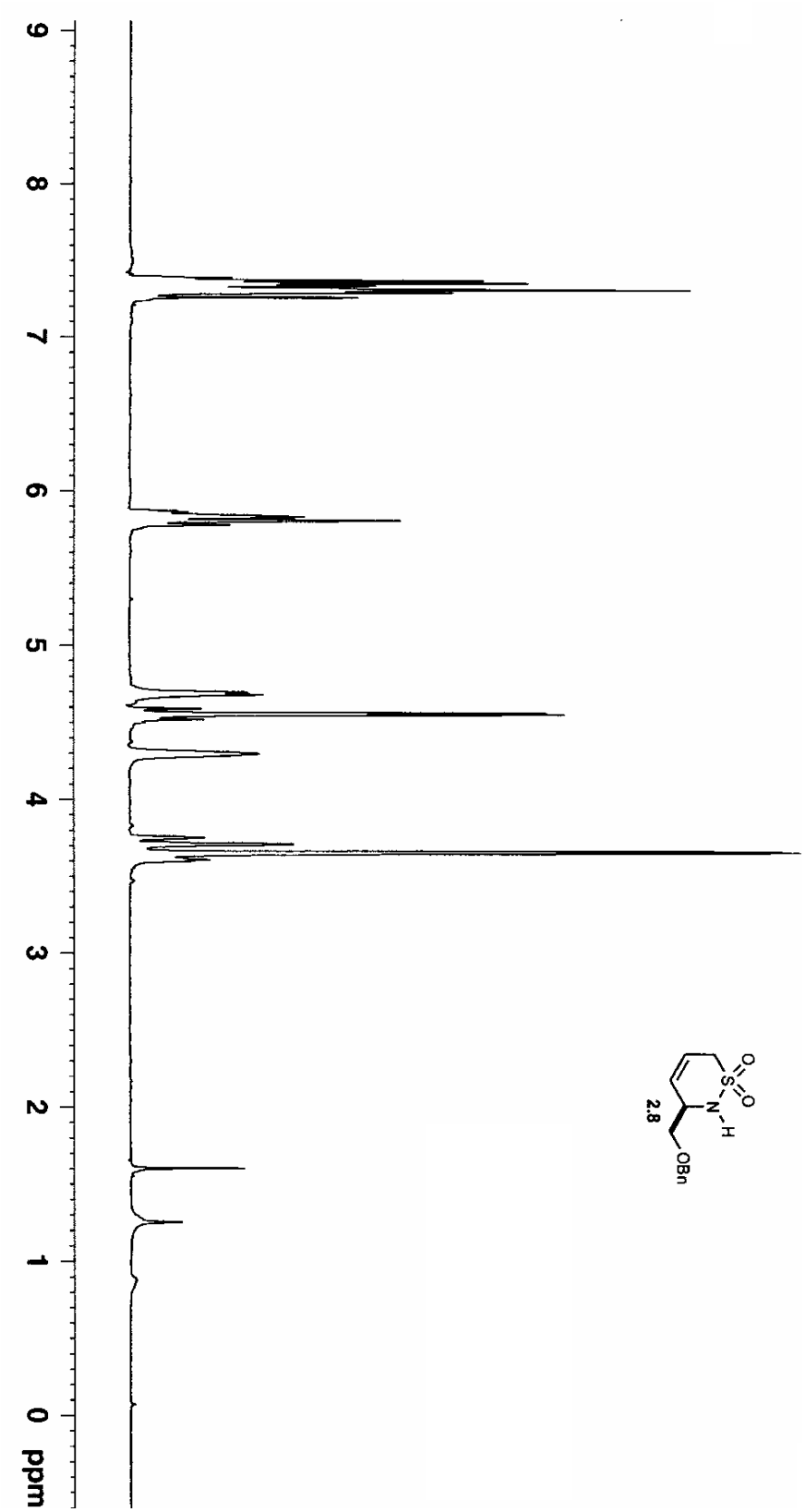
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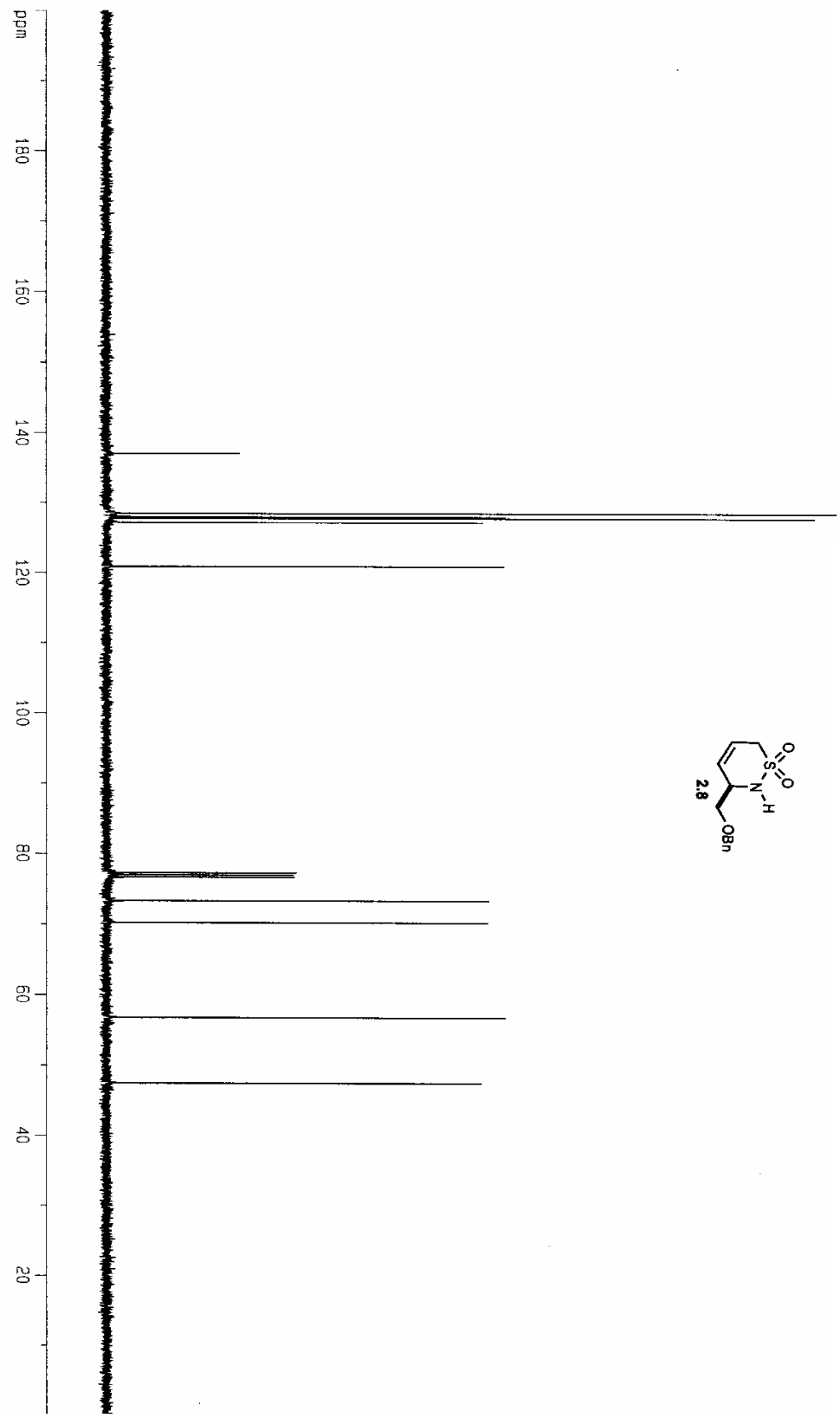
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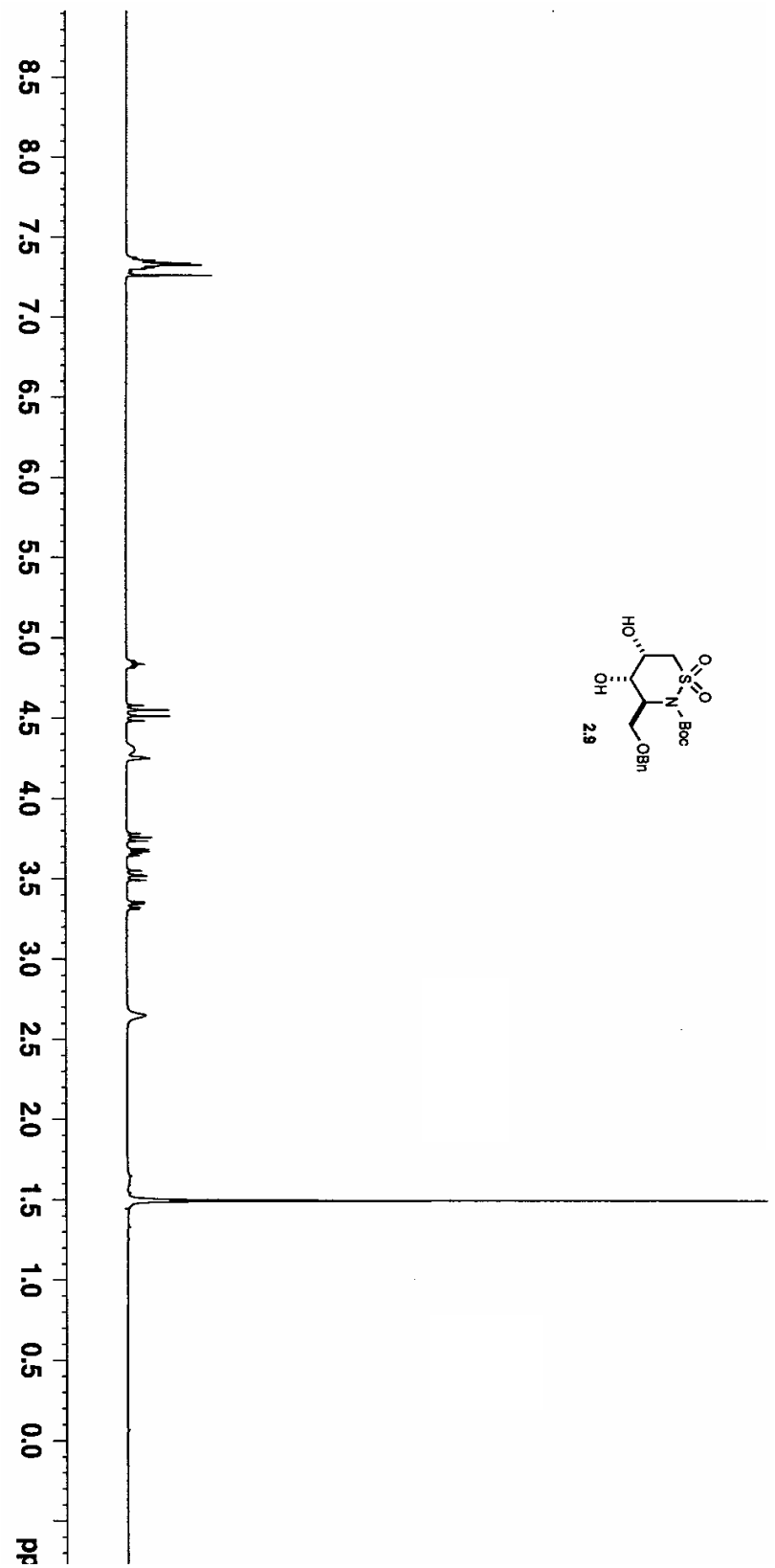
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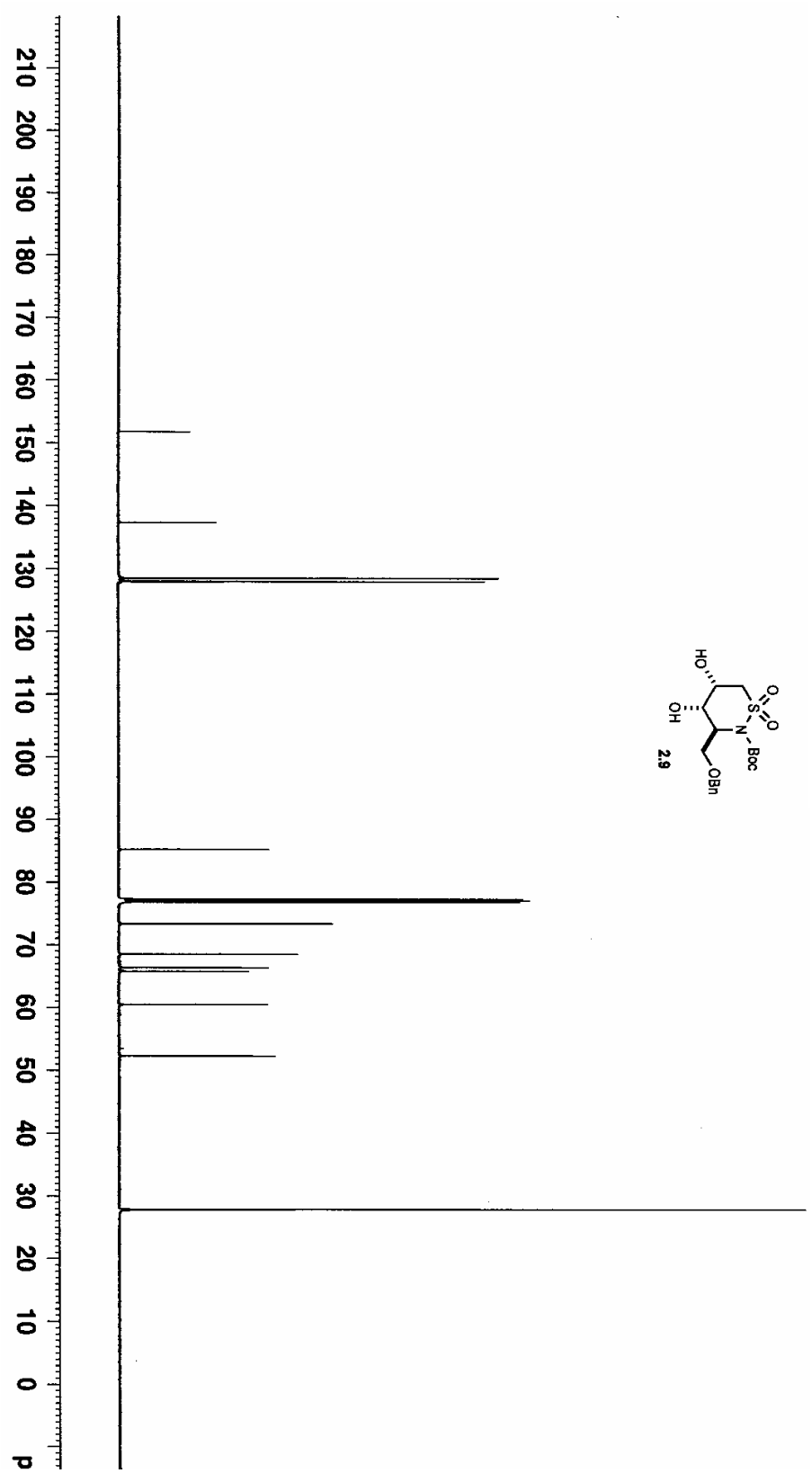
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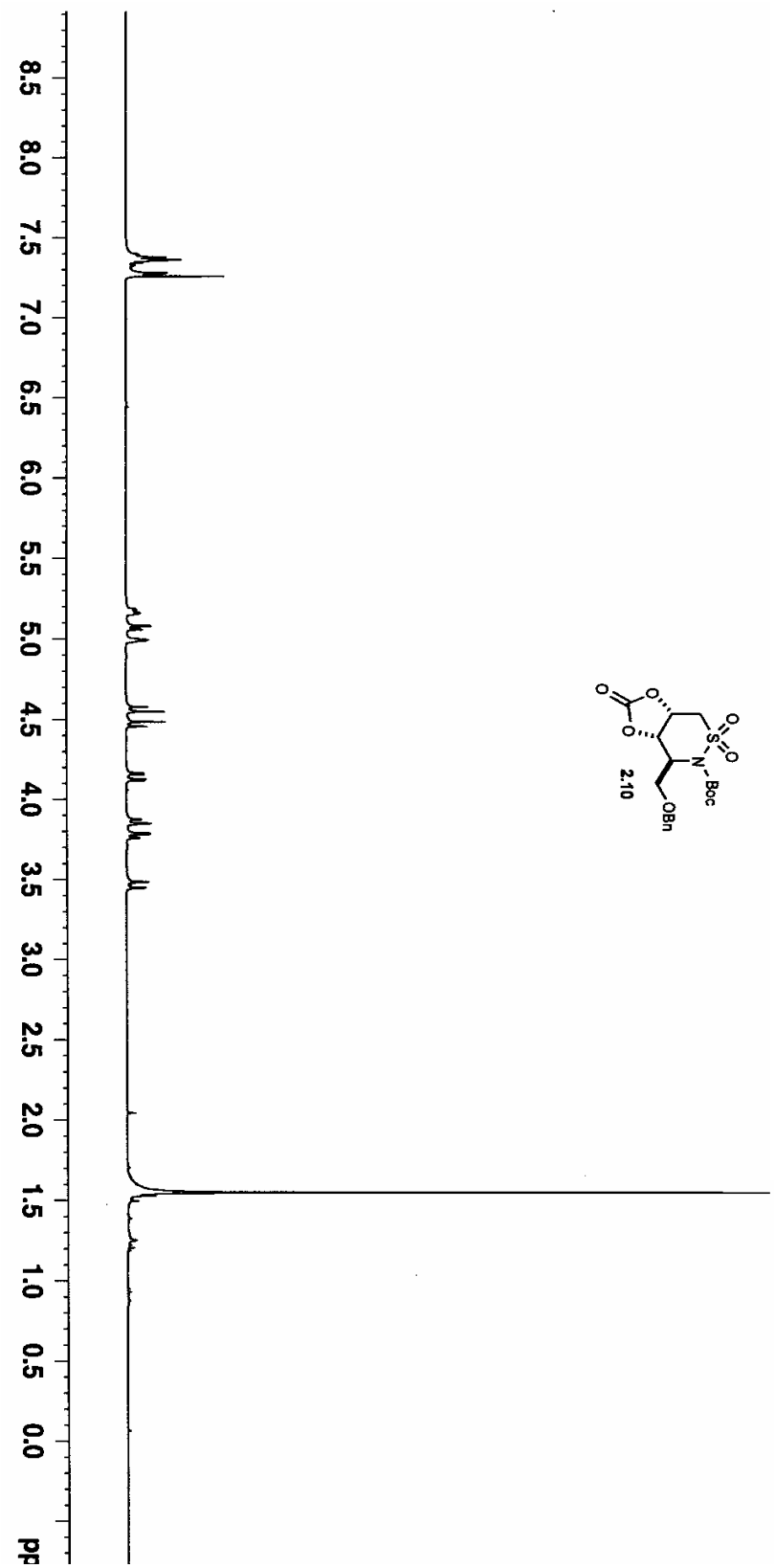
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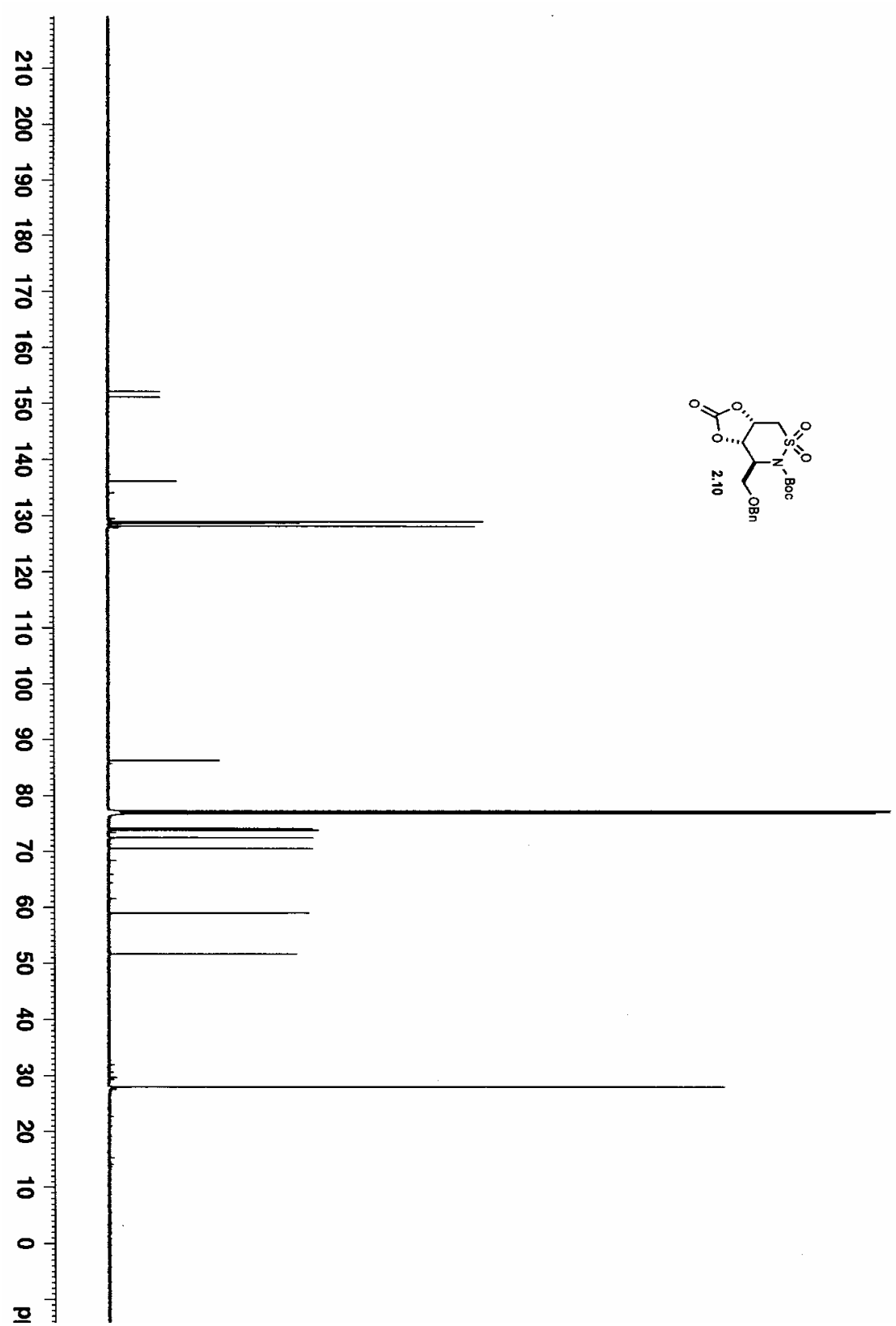
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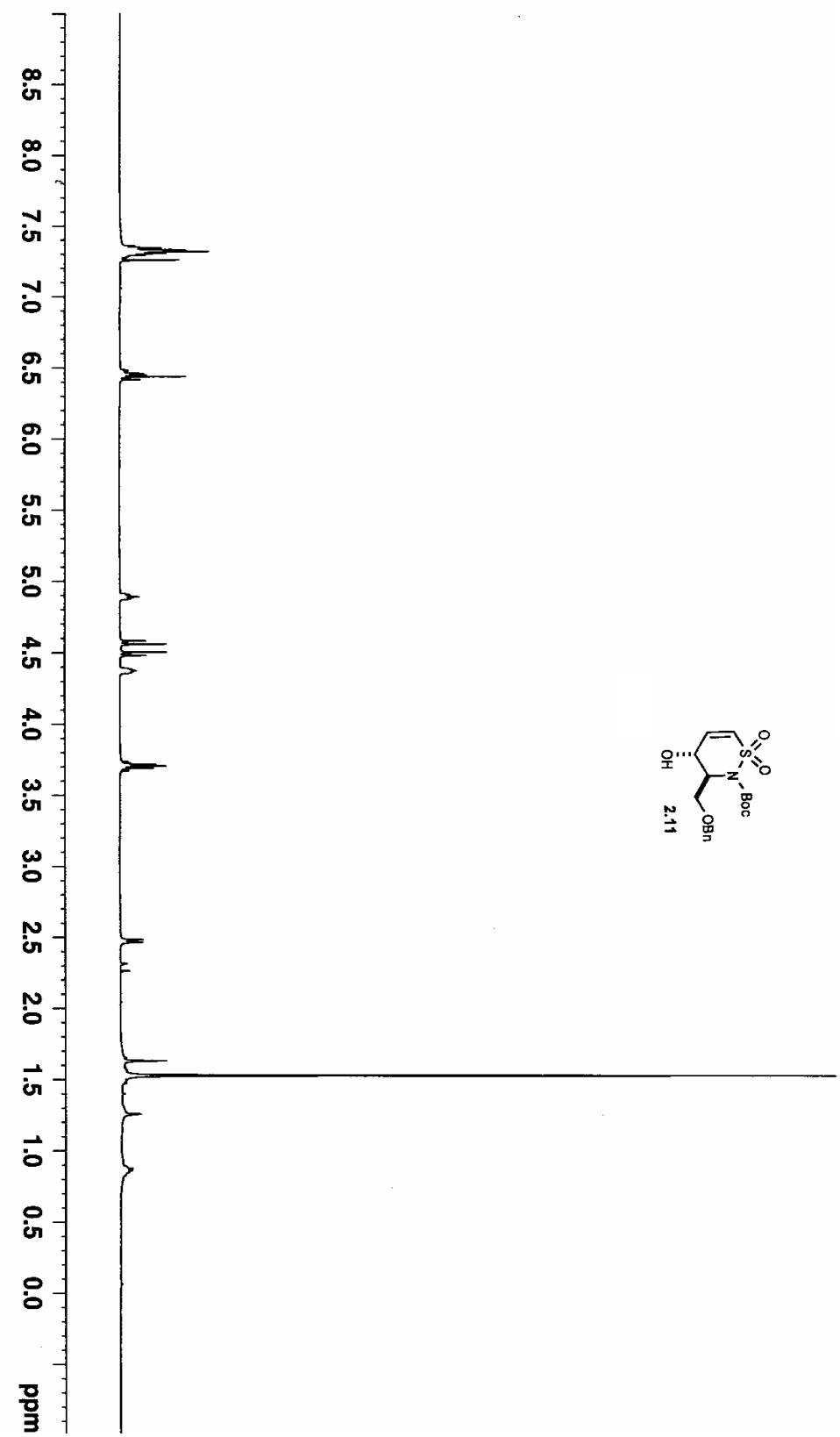
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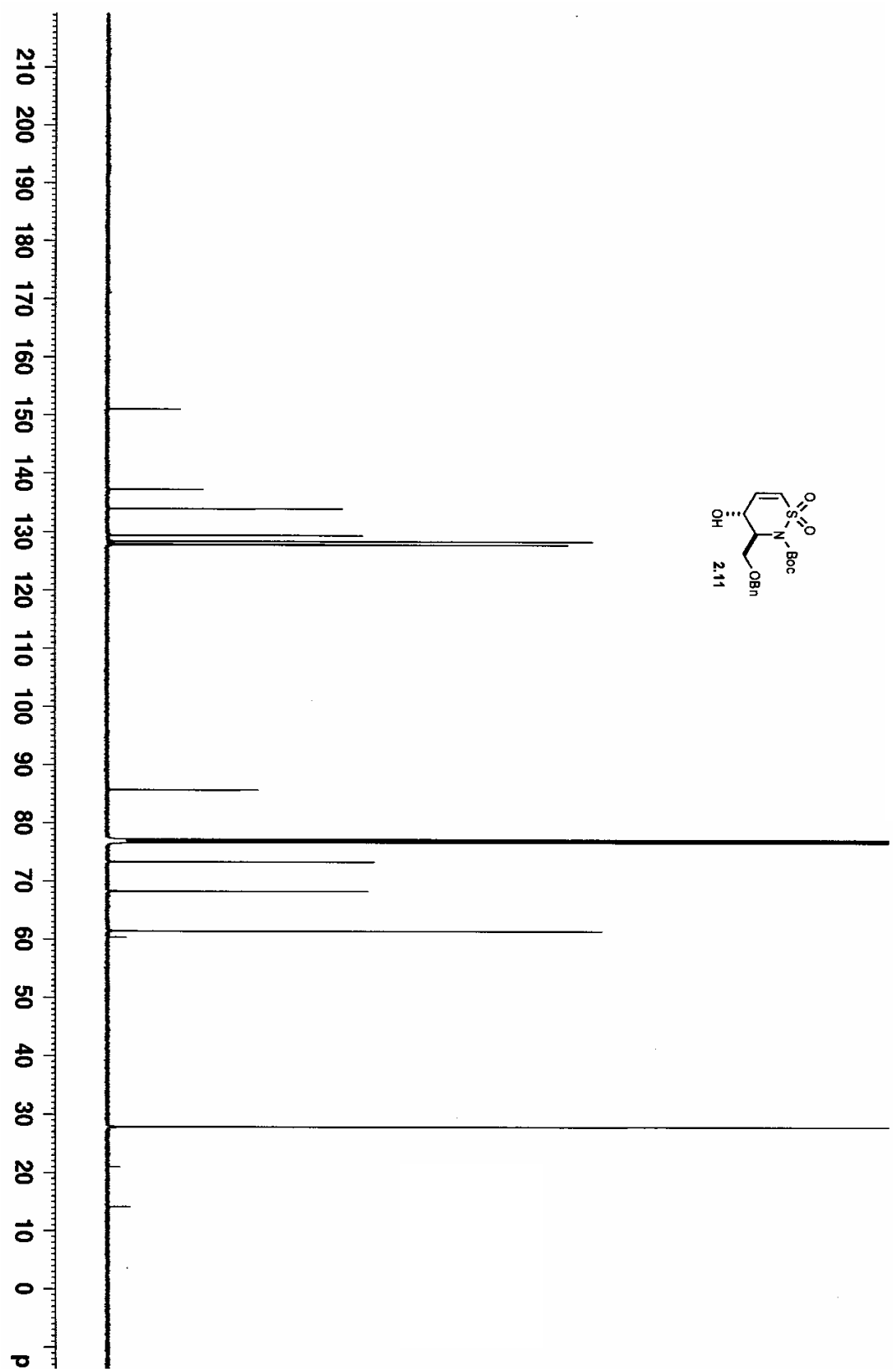
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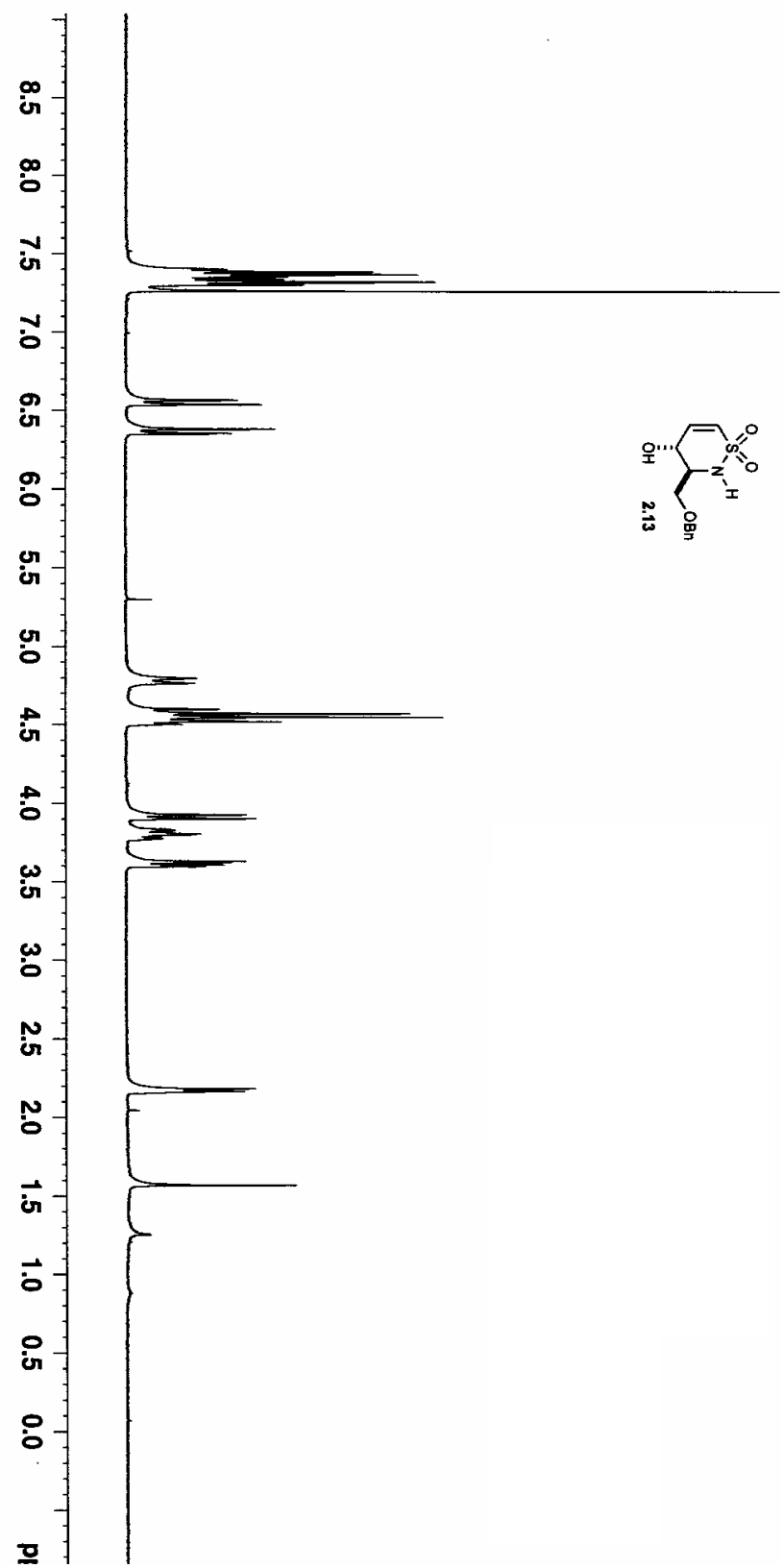
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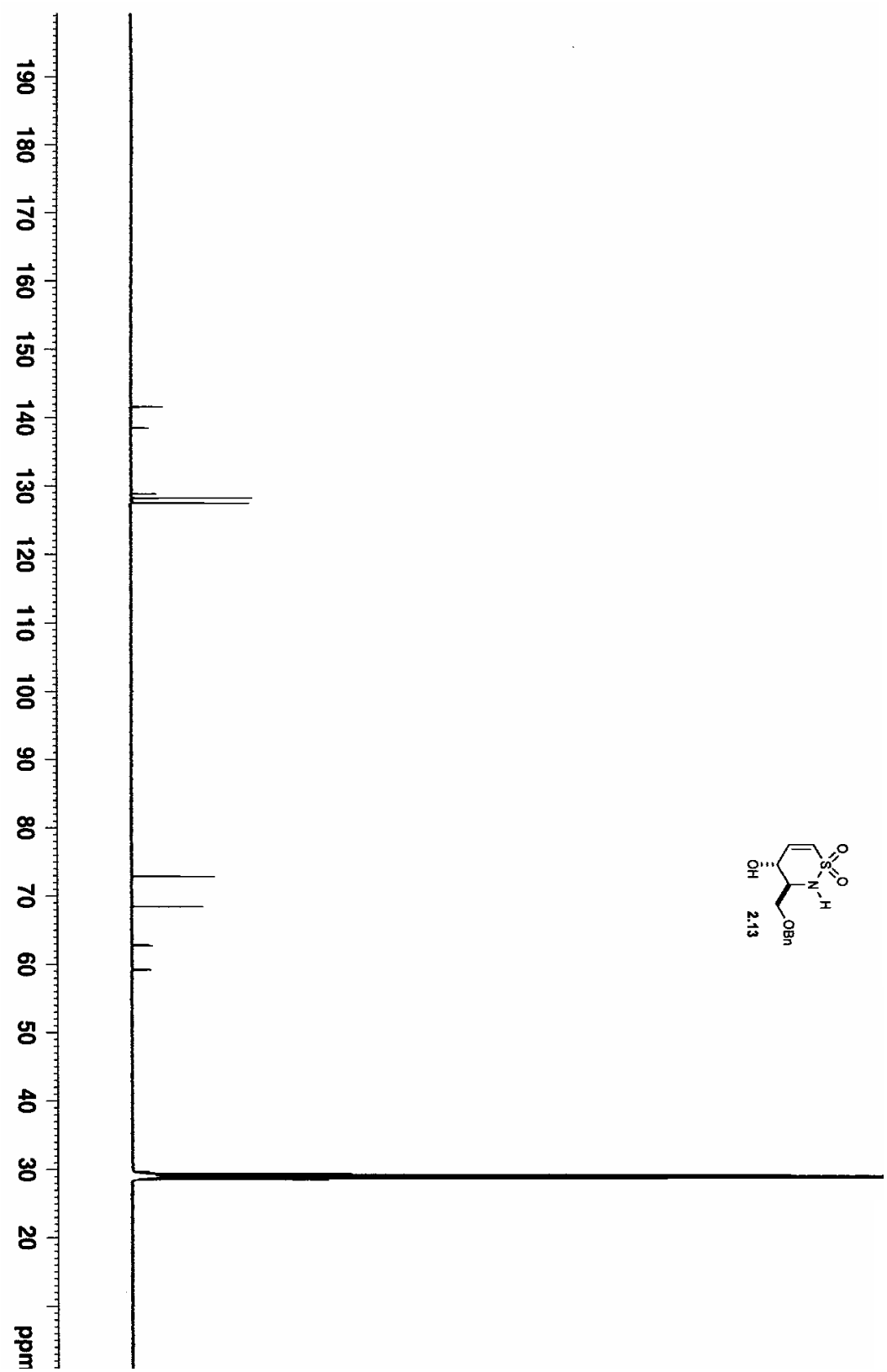
OBn
2.13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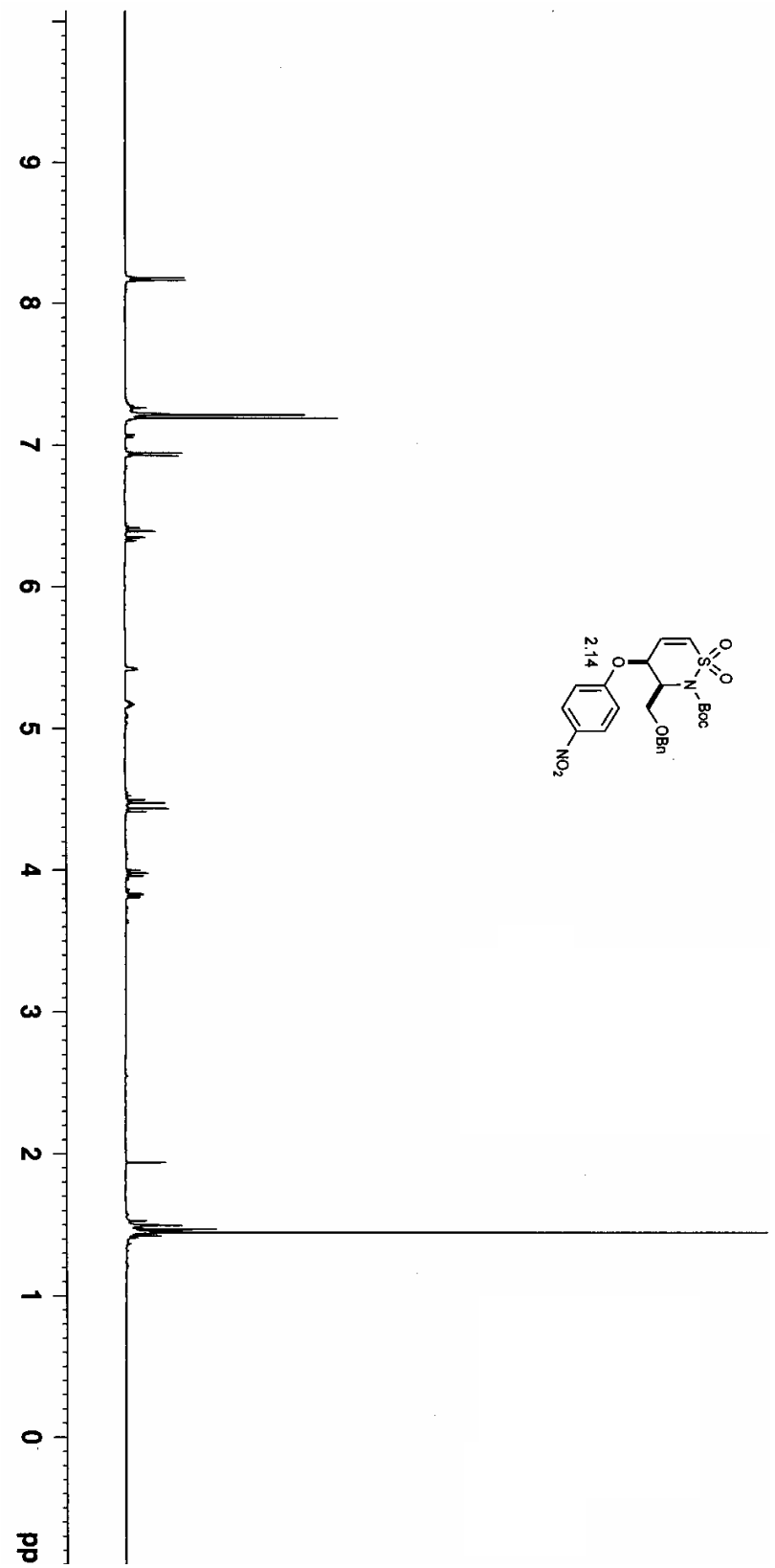
9
8
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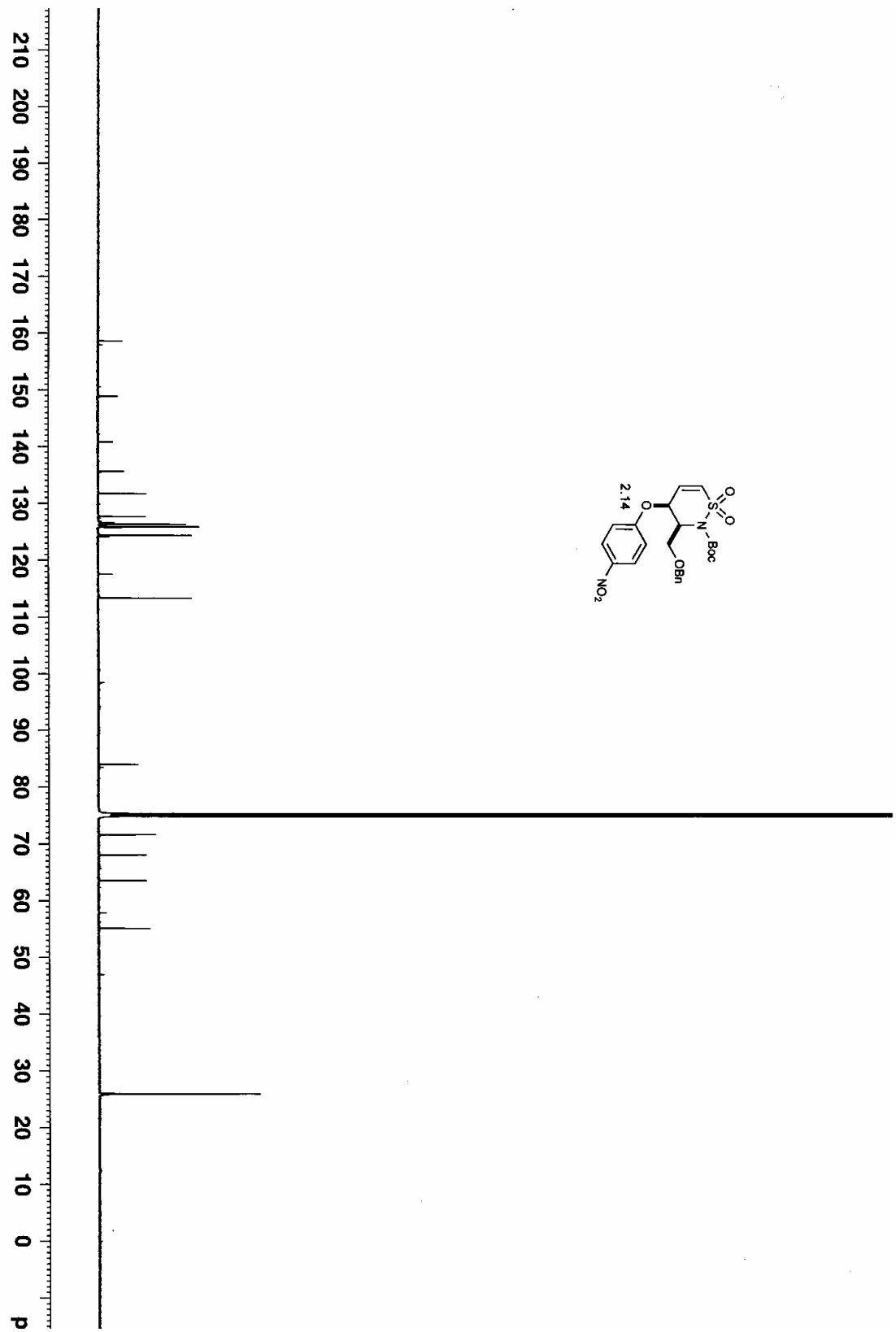
2
1
0
pp
2.14
O
S
O
O
N
Boc
OBn
NO2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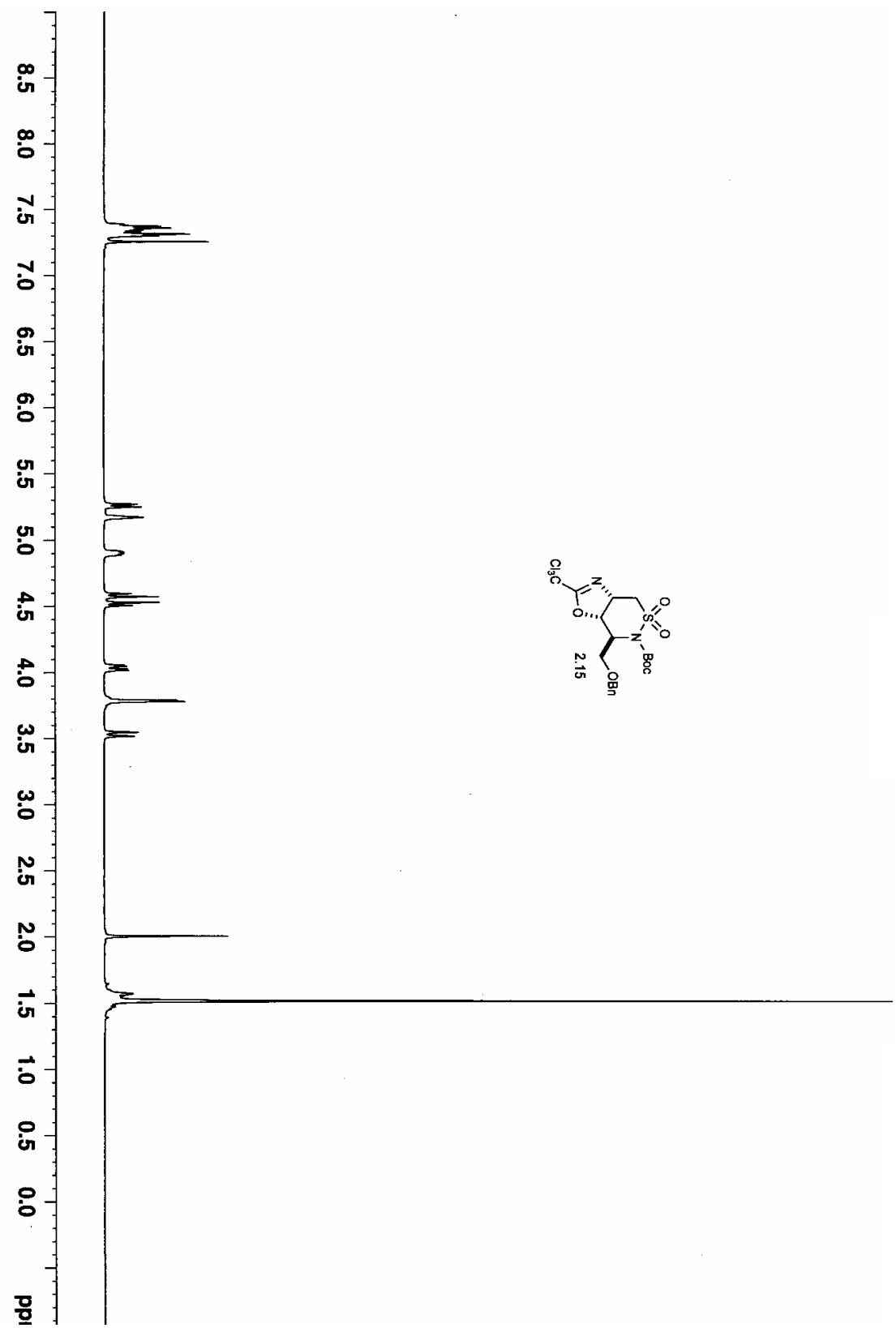
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3.0
2.5
2.0
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0.0
ppm
Cl3C
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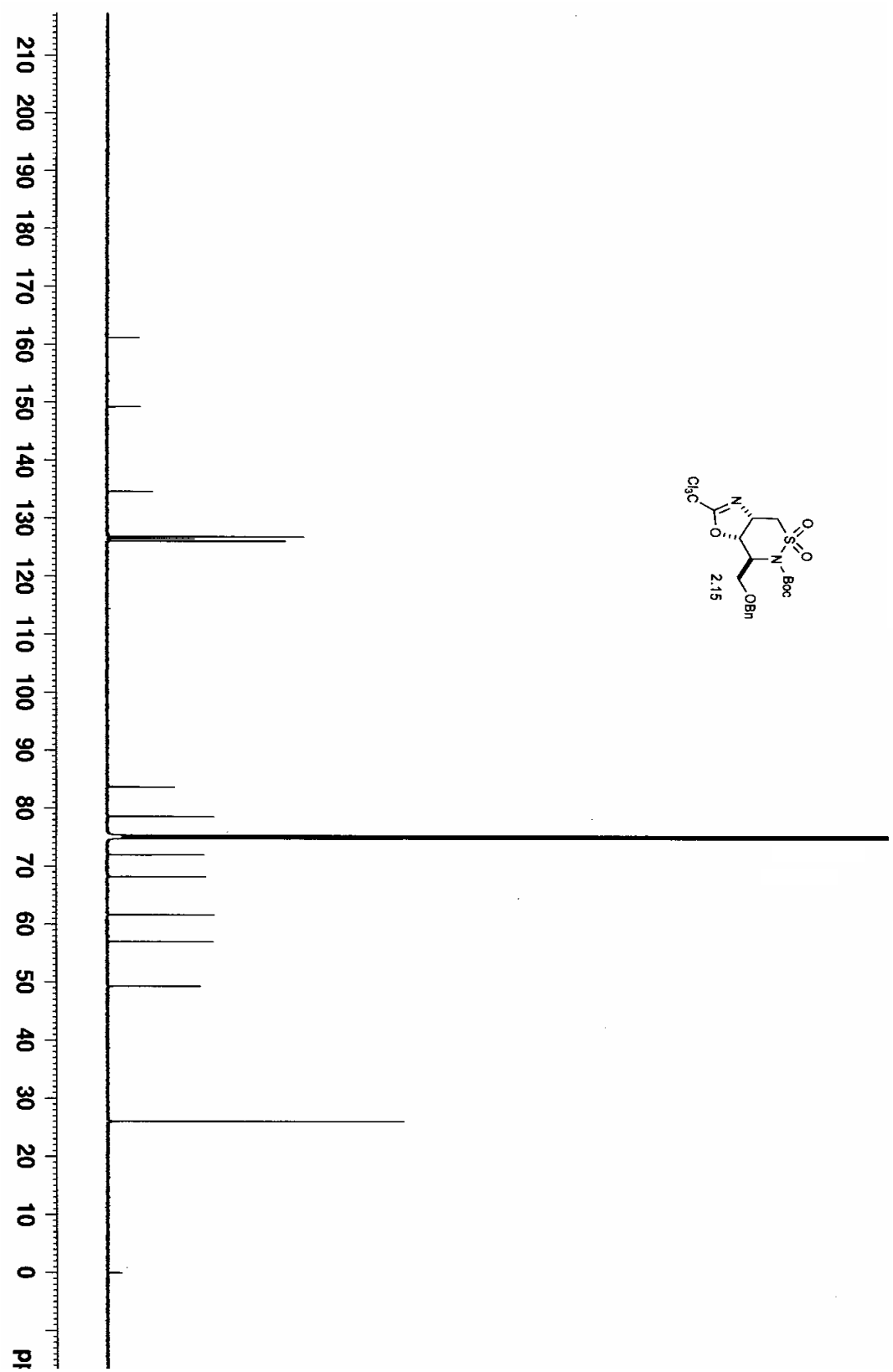
O
O
S
O
O
N
Boc
OBn
2.15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N
Boc
OBn
2.15
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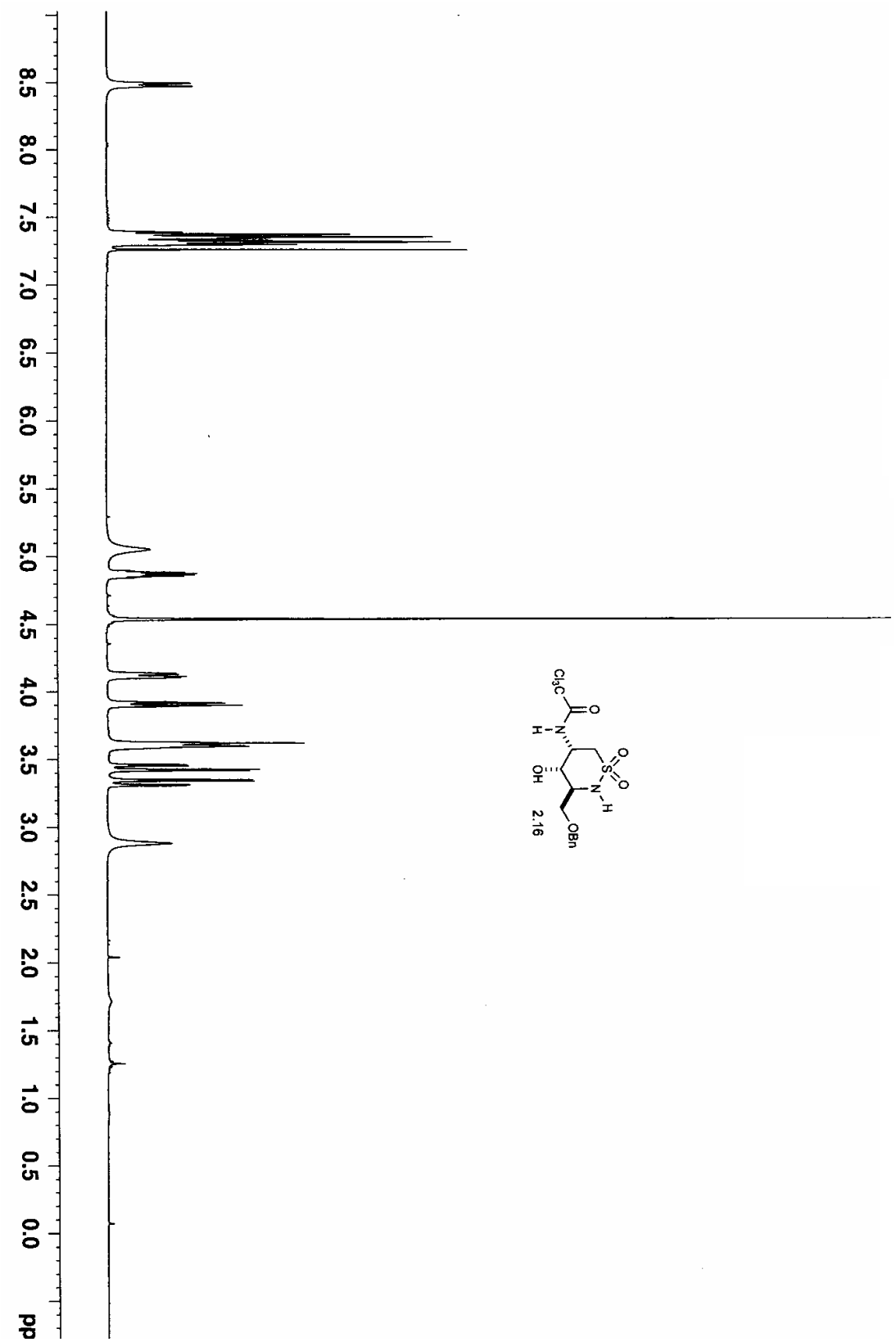
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1.5
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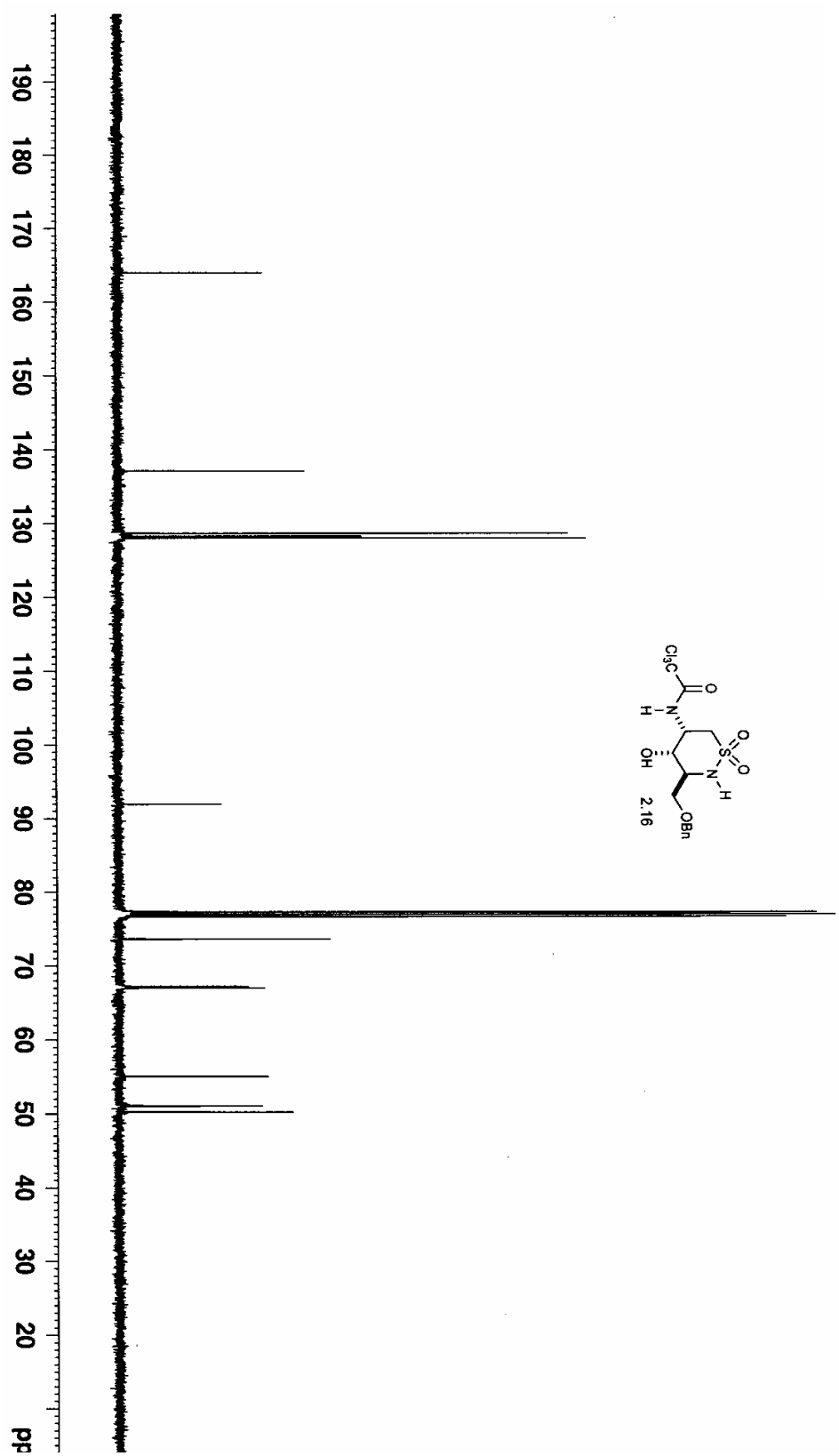
pp
Cl3C
O
N
H
OH
2.16
S
O
O
N
H
OBn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pp
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H
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S
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N
H
OH
2.16
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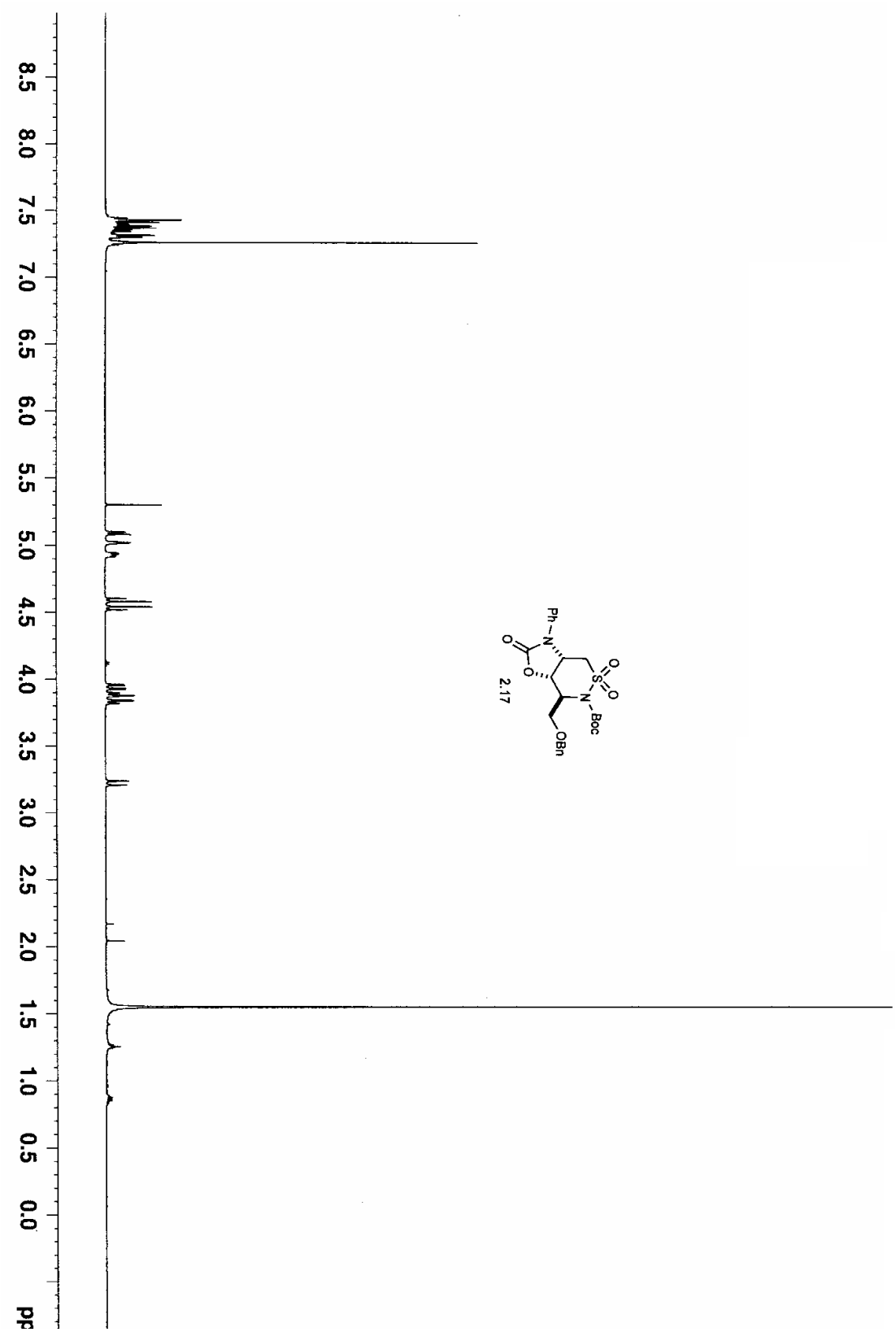
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4.0
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2.5
2.0
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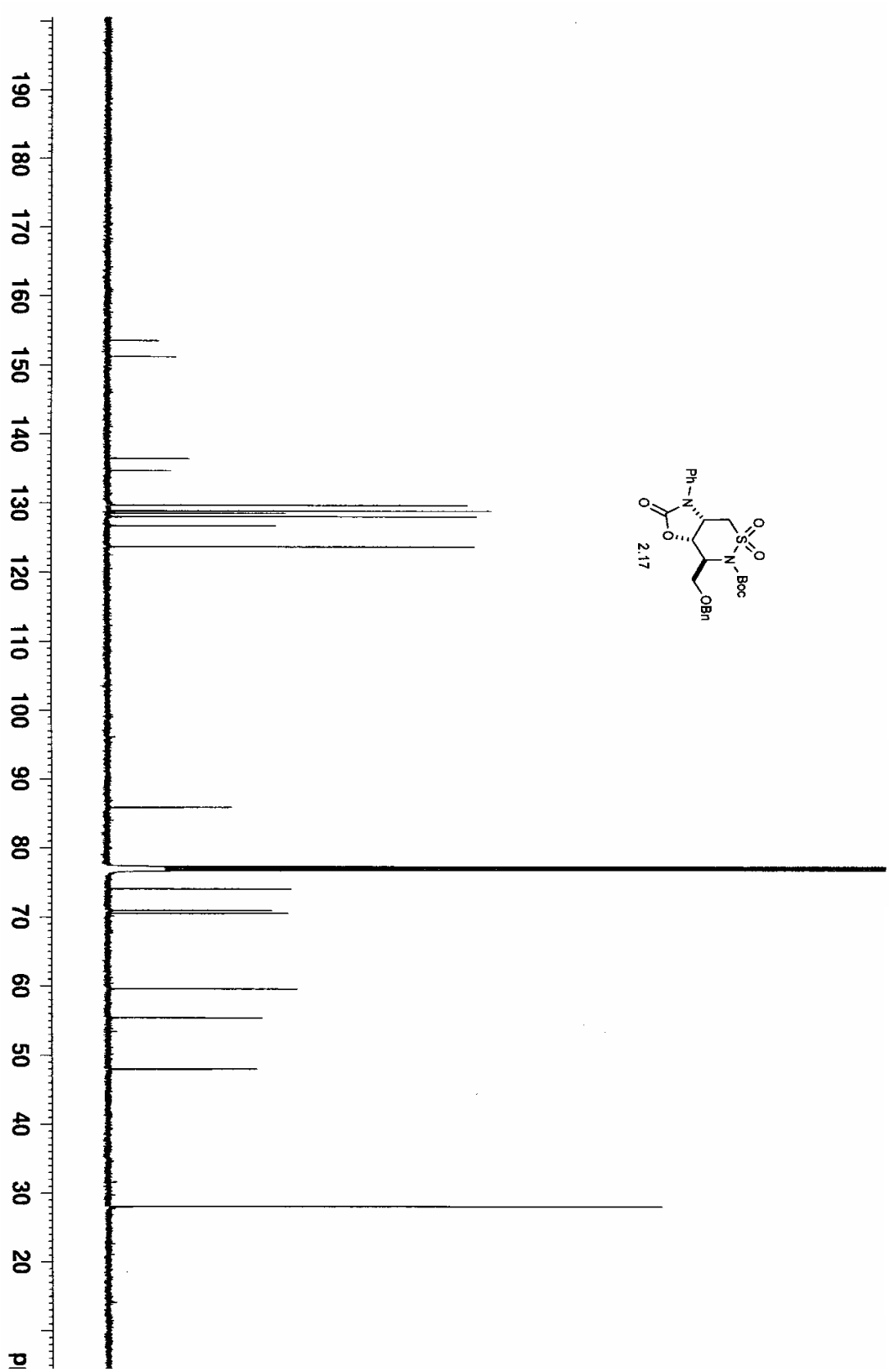
0.0
Ph
N
O
O
O
S
O
O
N
Boc
OBn
2.17


Ph
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O
O
O
S
O
O
N
Boc
OBn
2.17
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150
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120
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80
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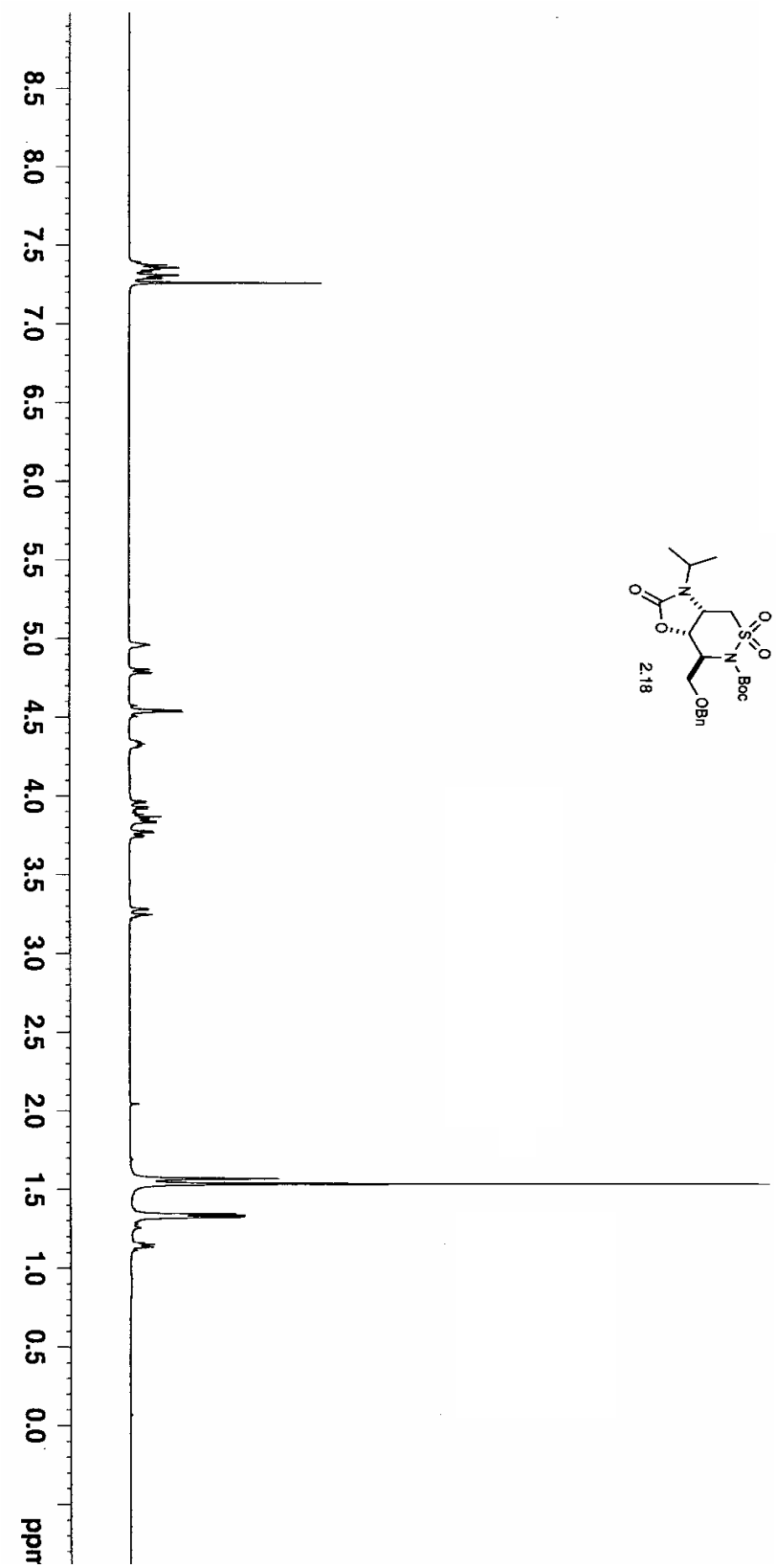
20
pl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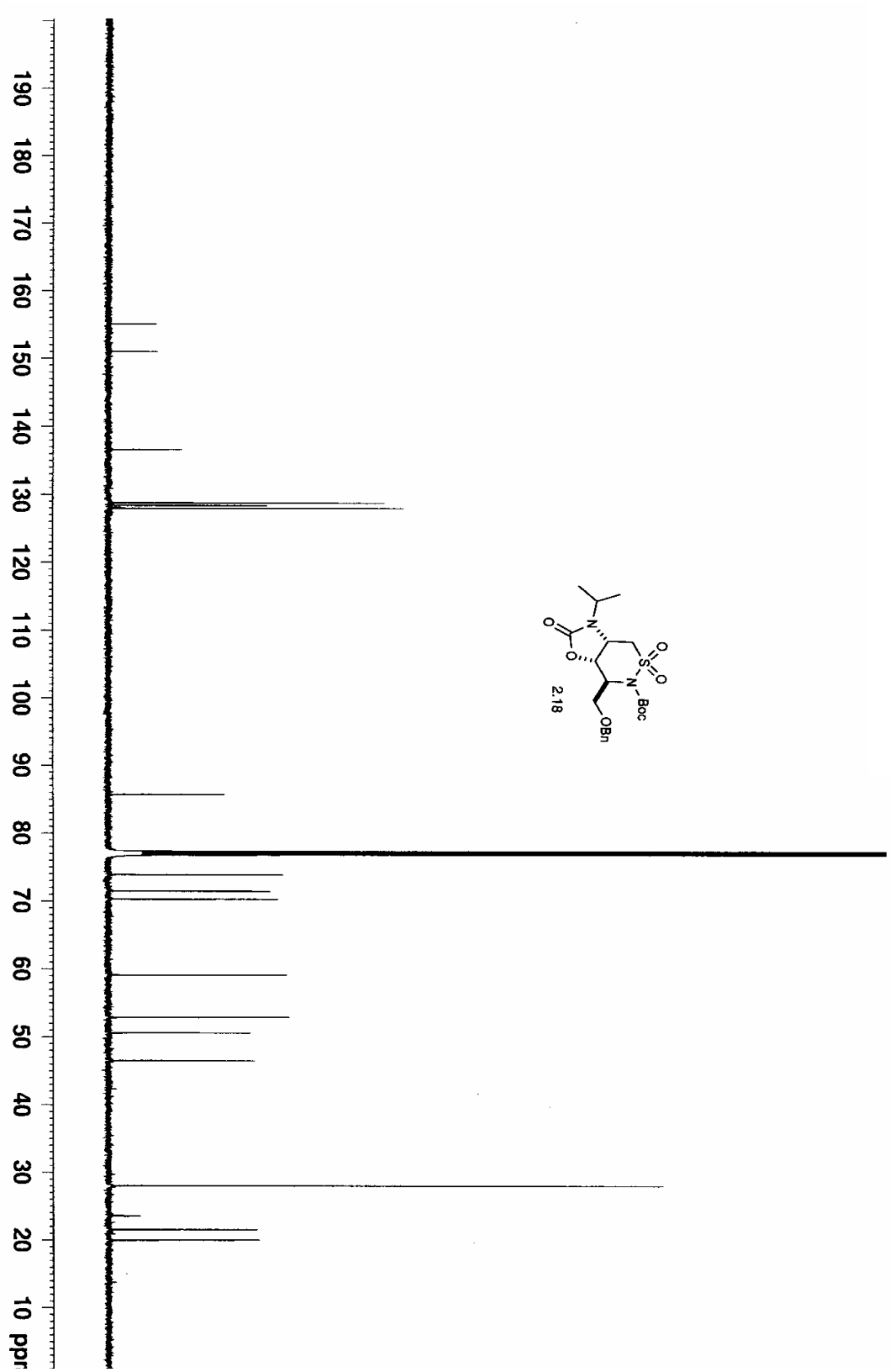
0.0
ppm
2.18
Boc
OBn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30
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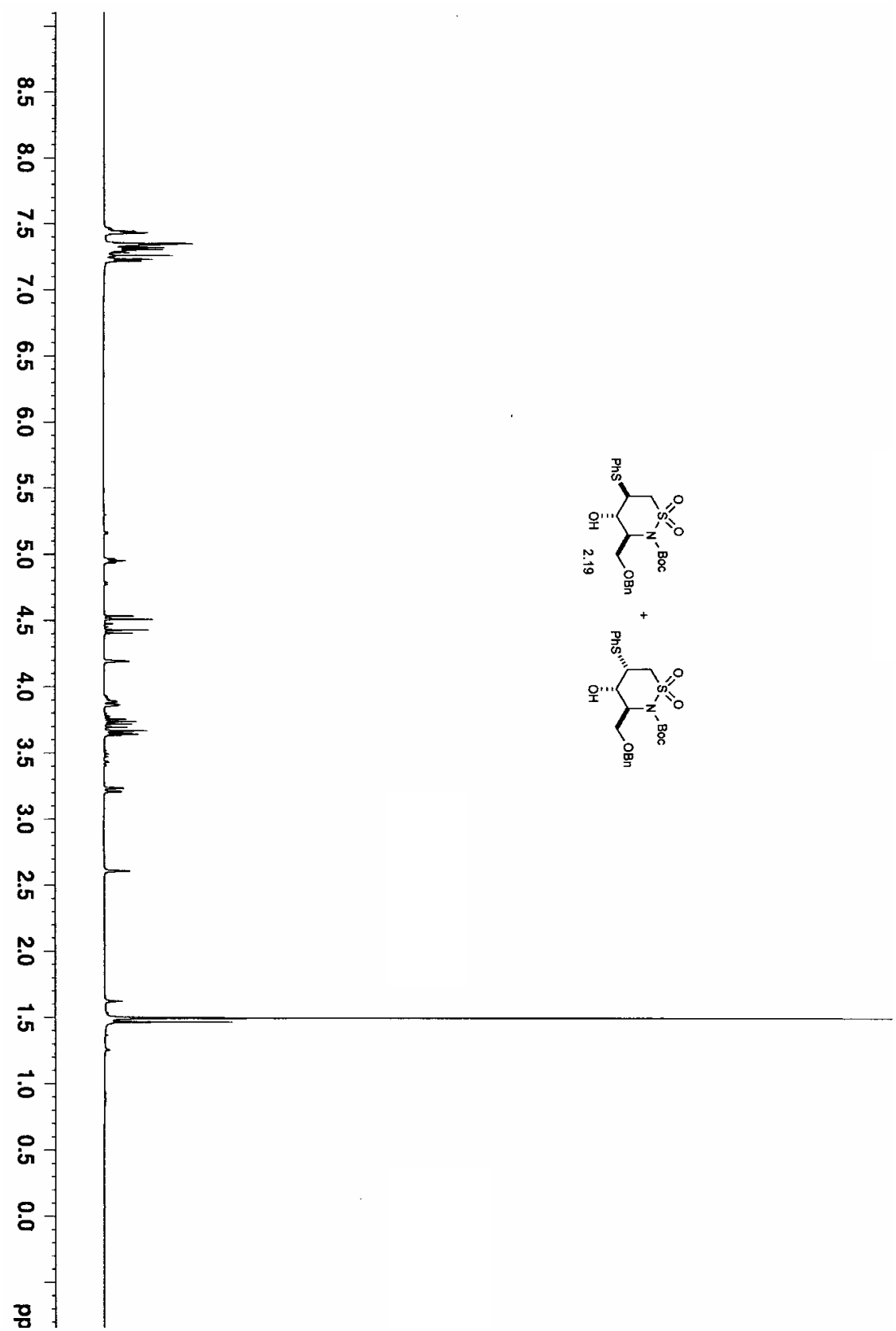
10 ppm
2.18
Boc
OBn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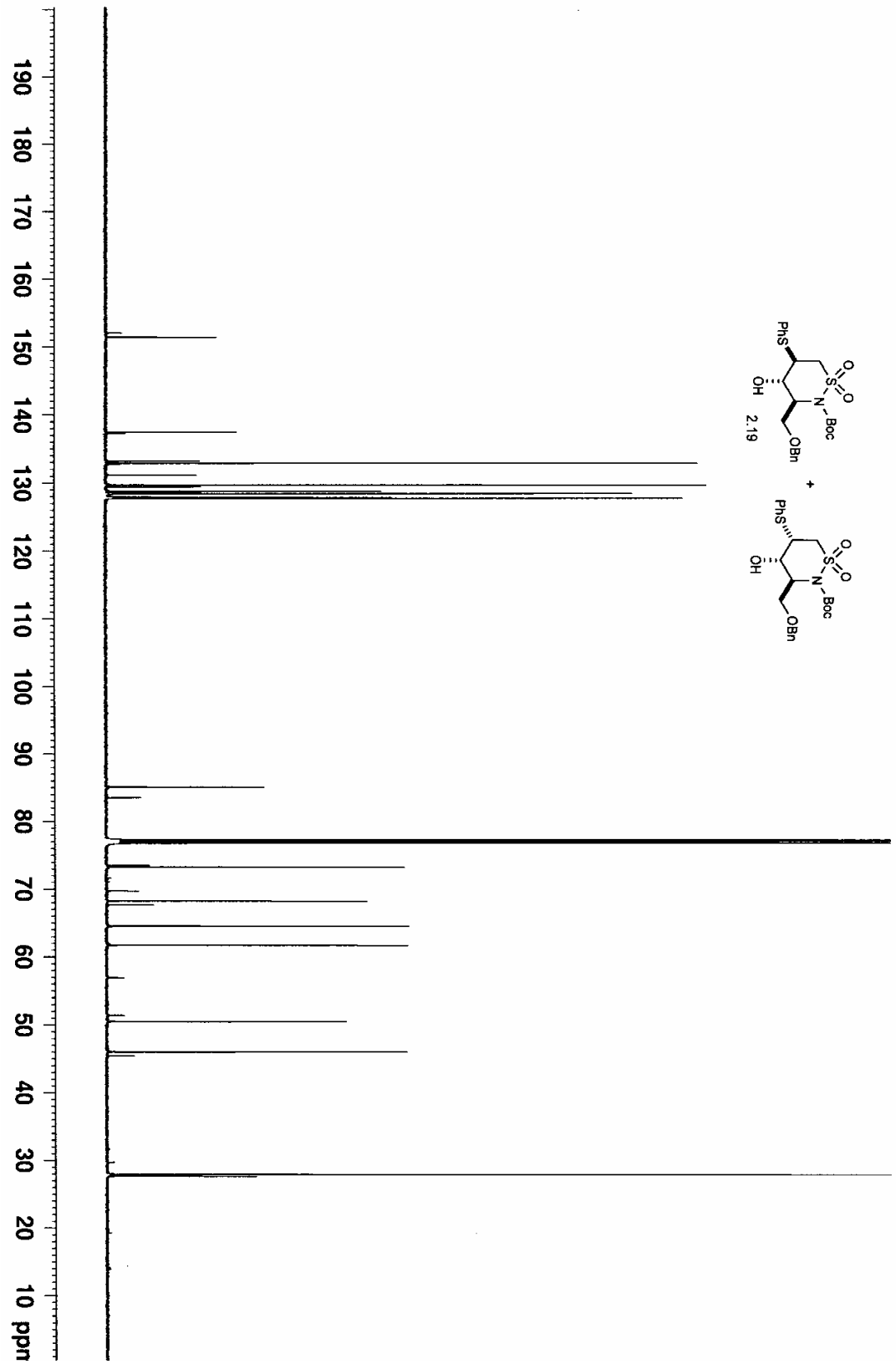
3.0
2.5
2.0
1.5
1.0
0.5
0.0
pp
PhS
OH
2.19
O
S
N
Boc
OBn
+
PhS
OH
O
S
N
Boc
OBn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90
80
70
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30
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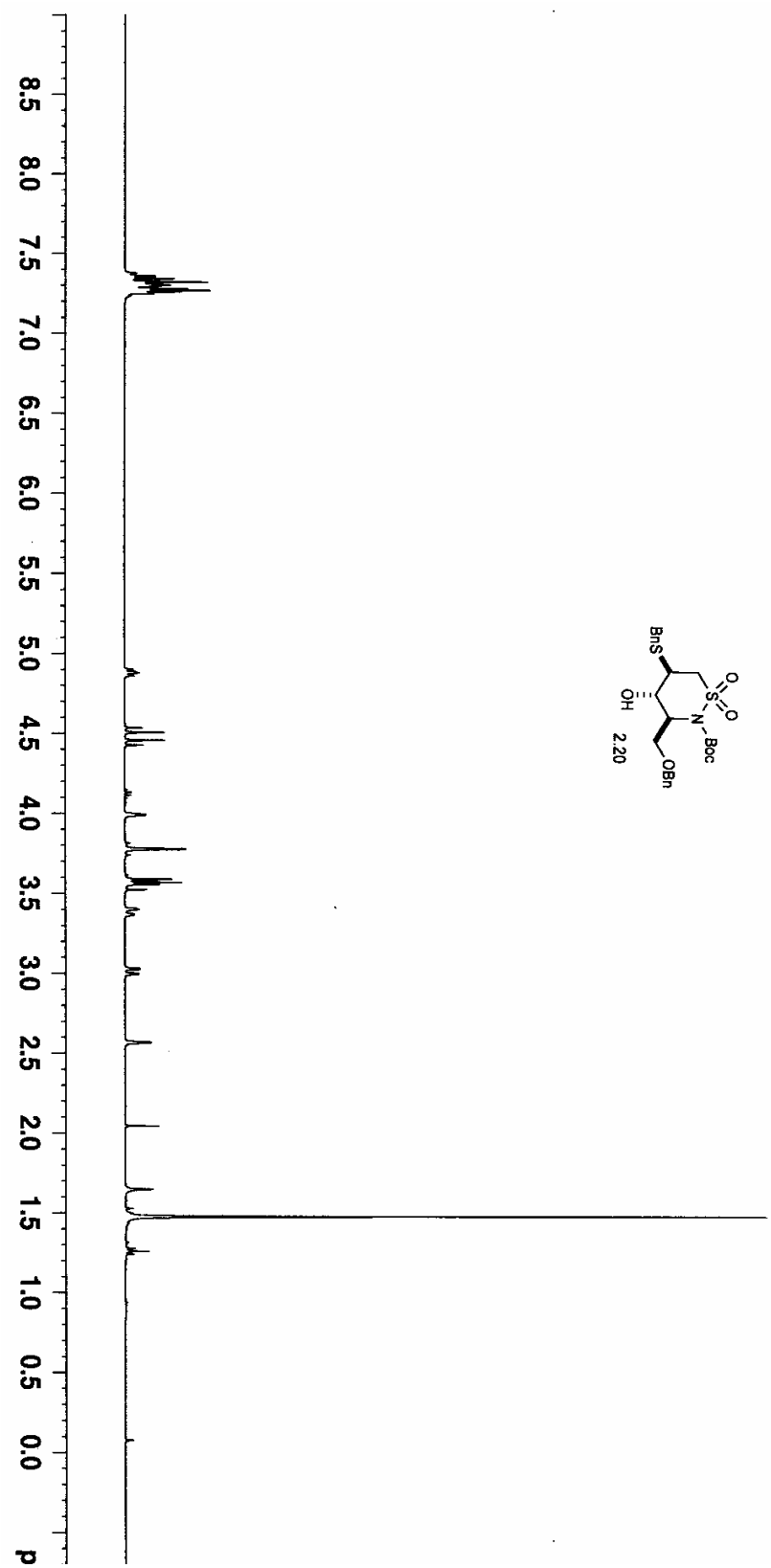
10 ppm
PhS
OH
2.19
N
Boc
OBn
+
PhS
OH
N
Boc
OBn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2.5
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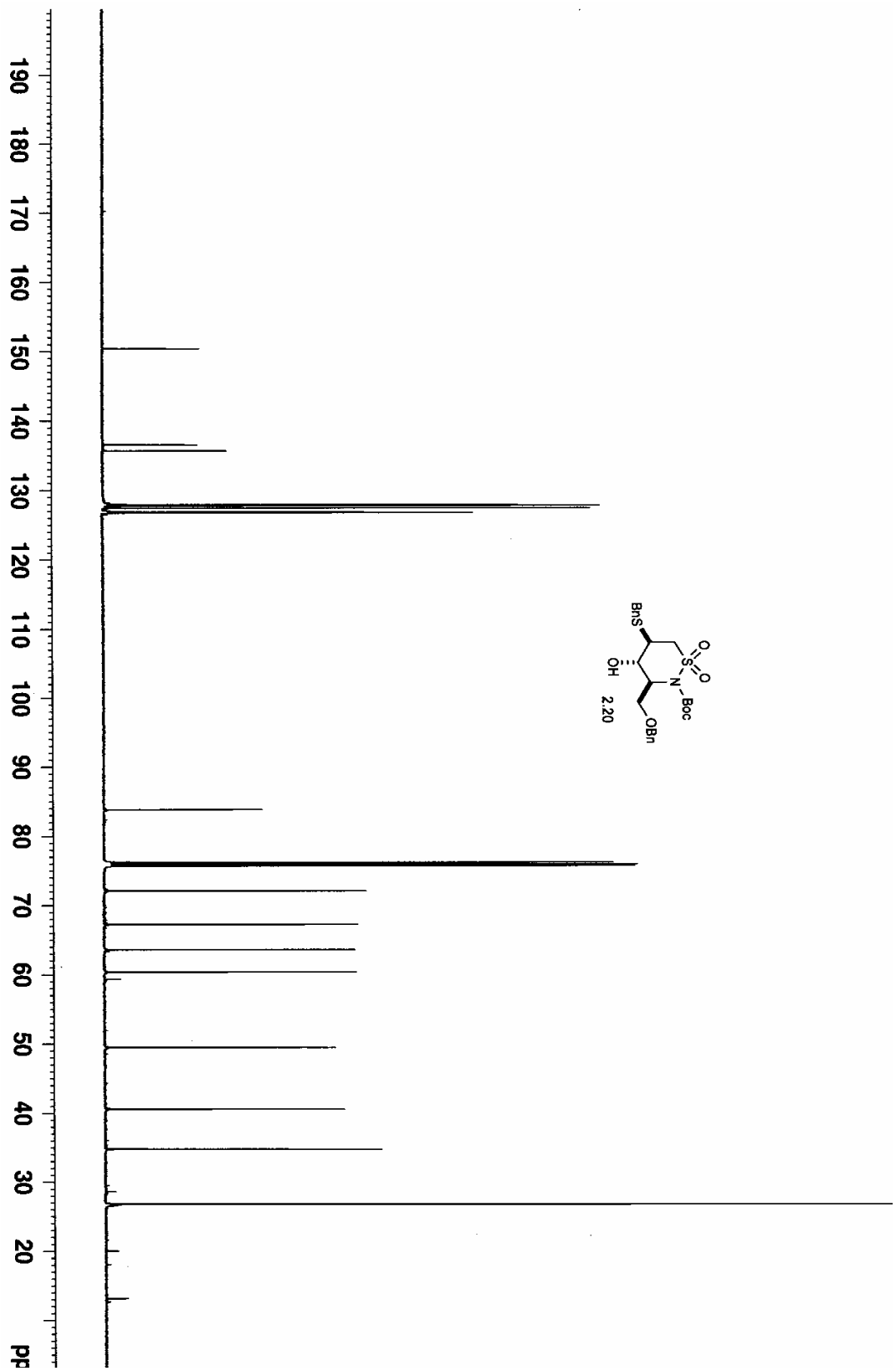
p
BnS
OH
2.20
O
S
O
N
Boc
OBn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Boc
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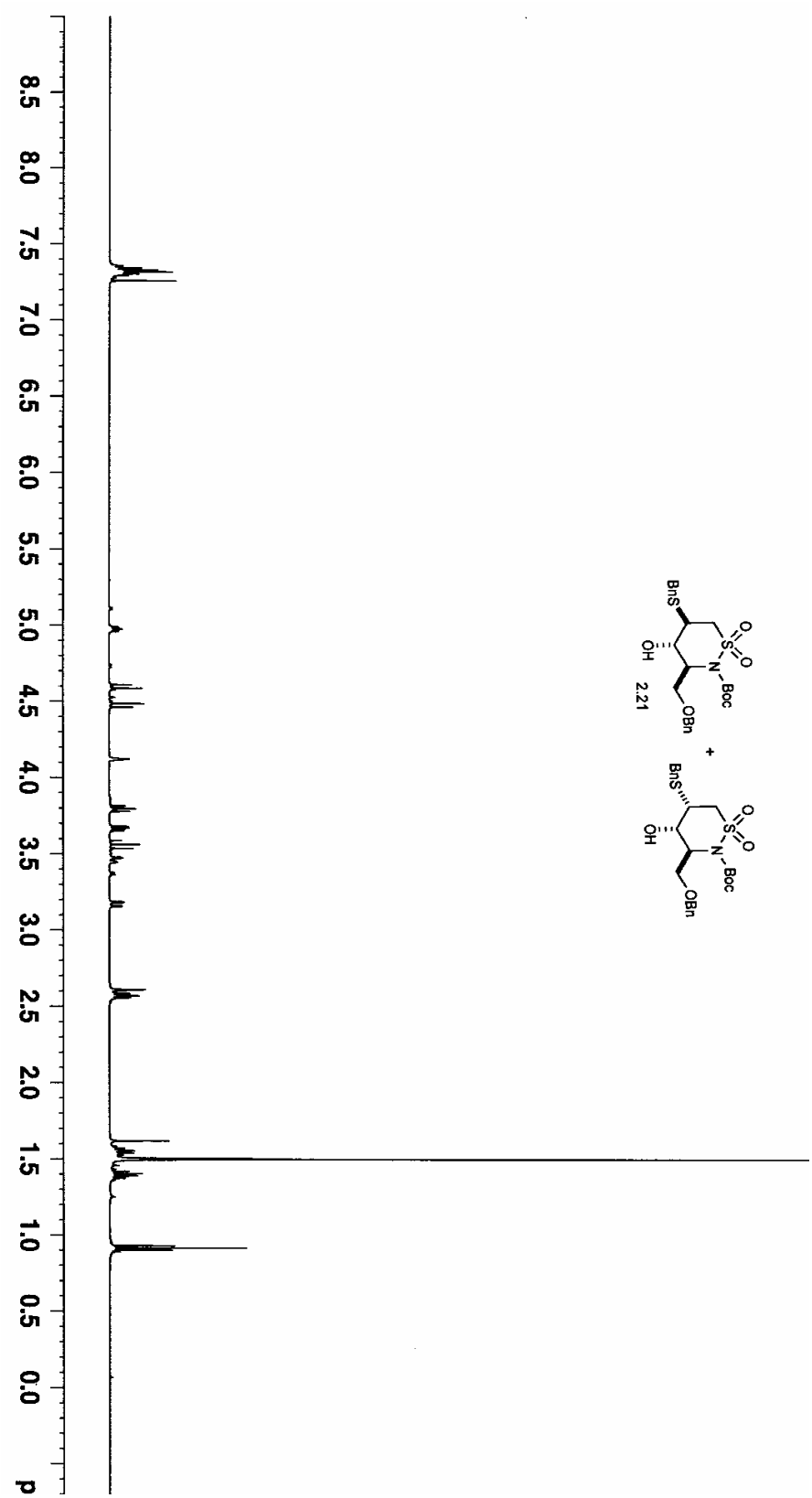
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4.0
3.5
3.0
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2.0
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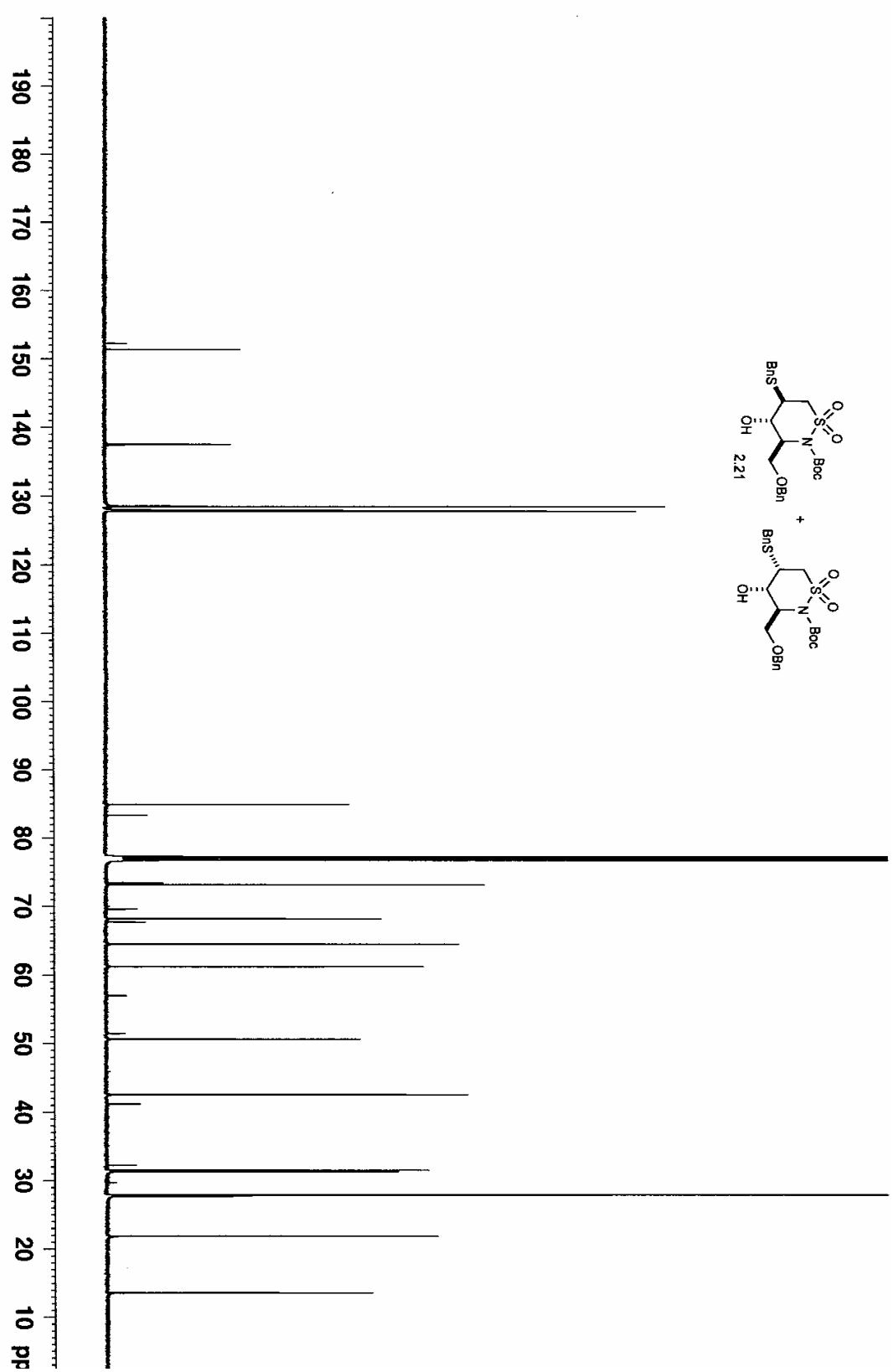
0.0
p
BnS
OH
2.21
Boc
OBn
+
BnS
OH
Boc
OBn


BnS
OH
2.21
OBn
Boc
N
S
O
O
+
BnS
OH
OBn
Boc
N
S
O
O
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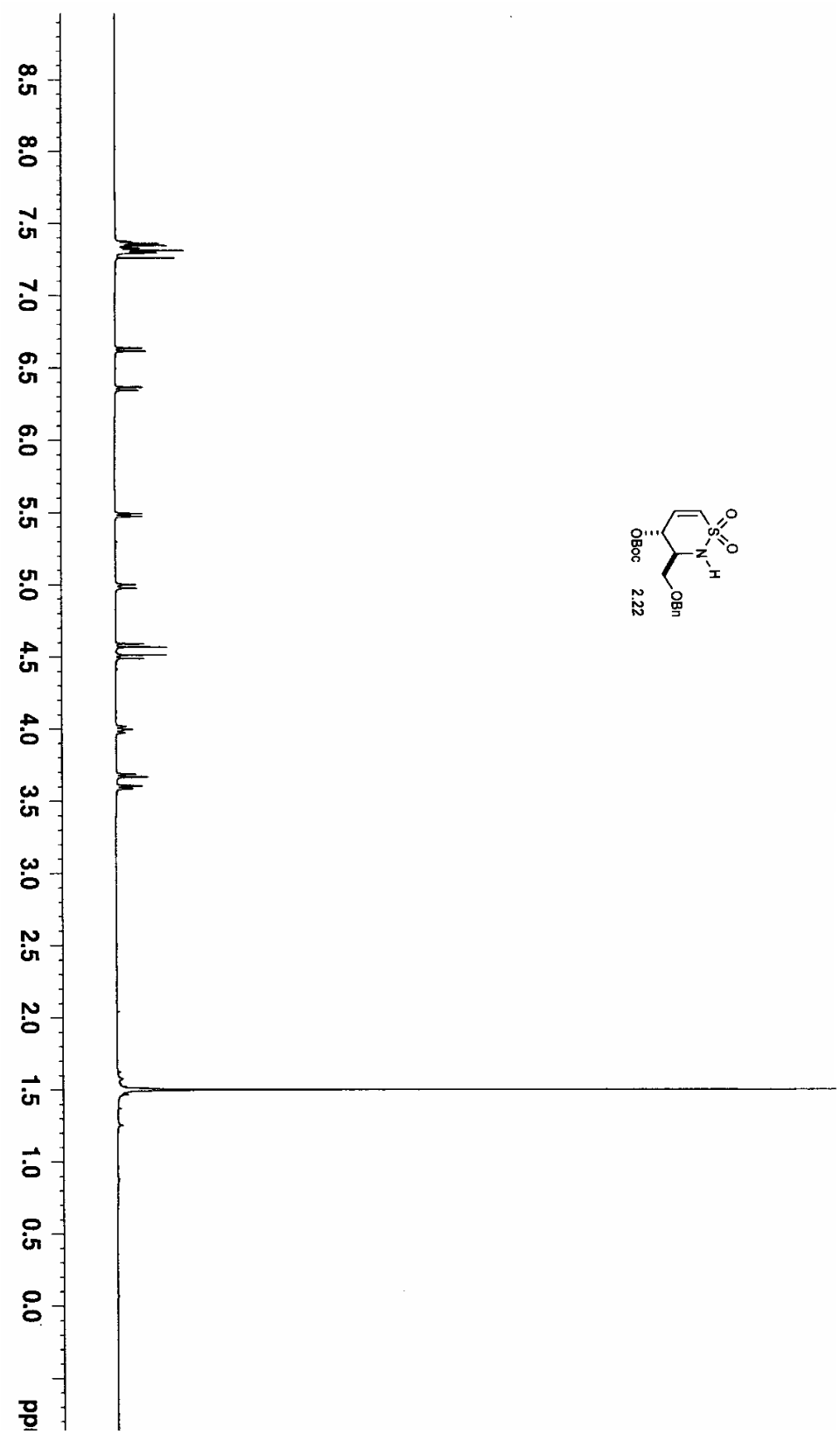
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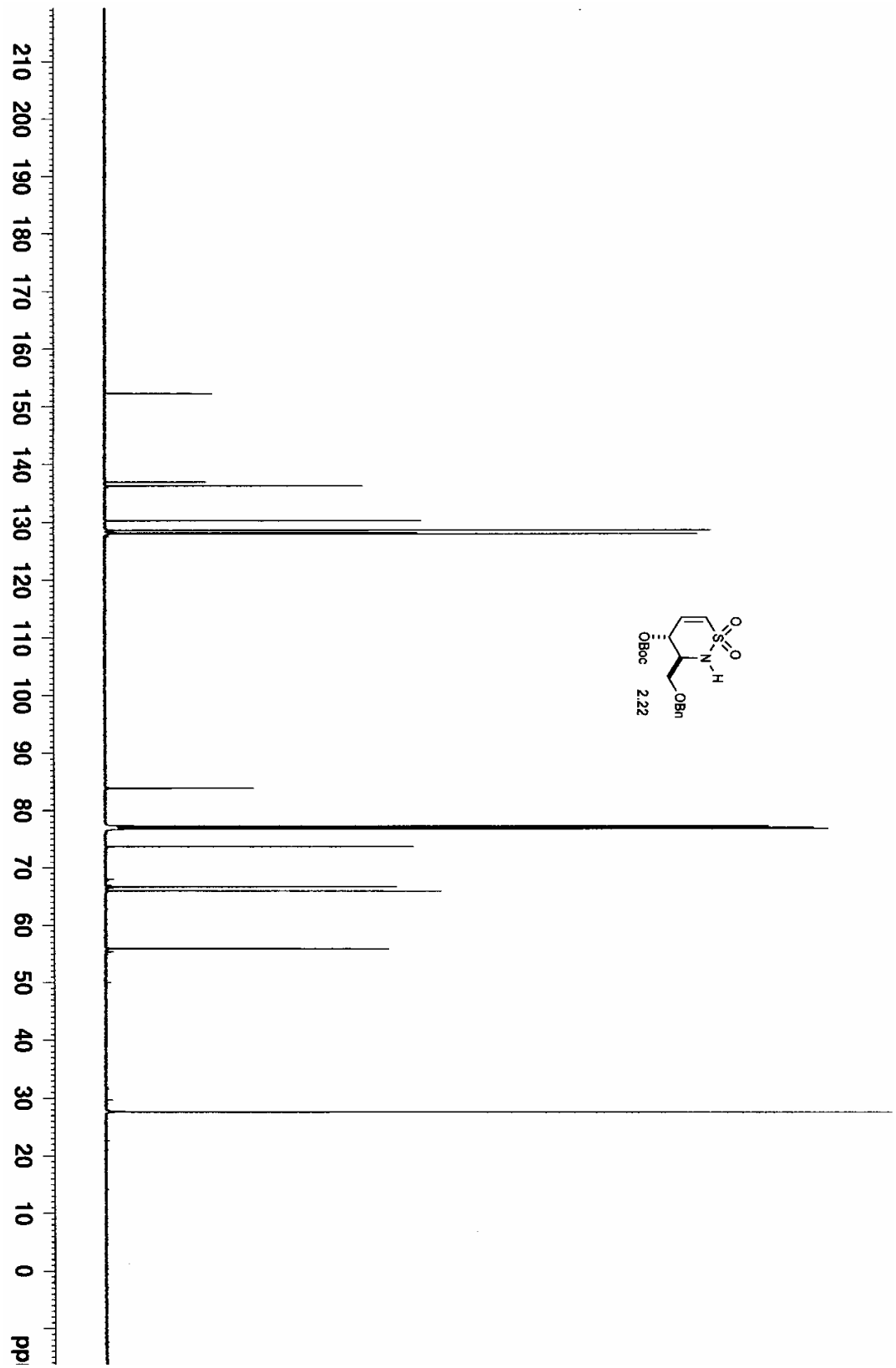
ppm
OBoc
OBn
2.22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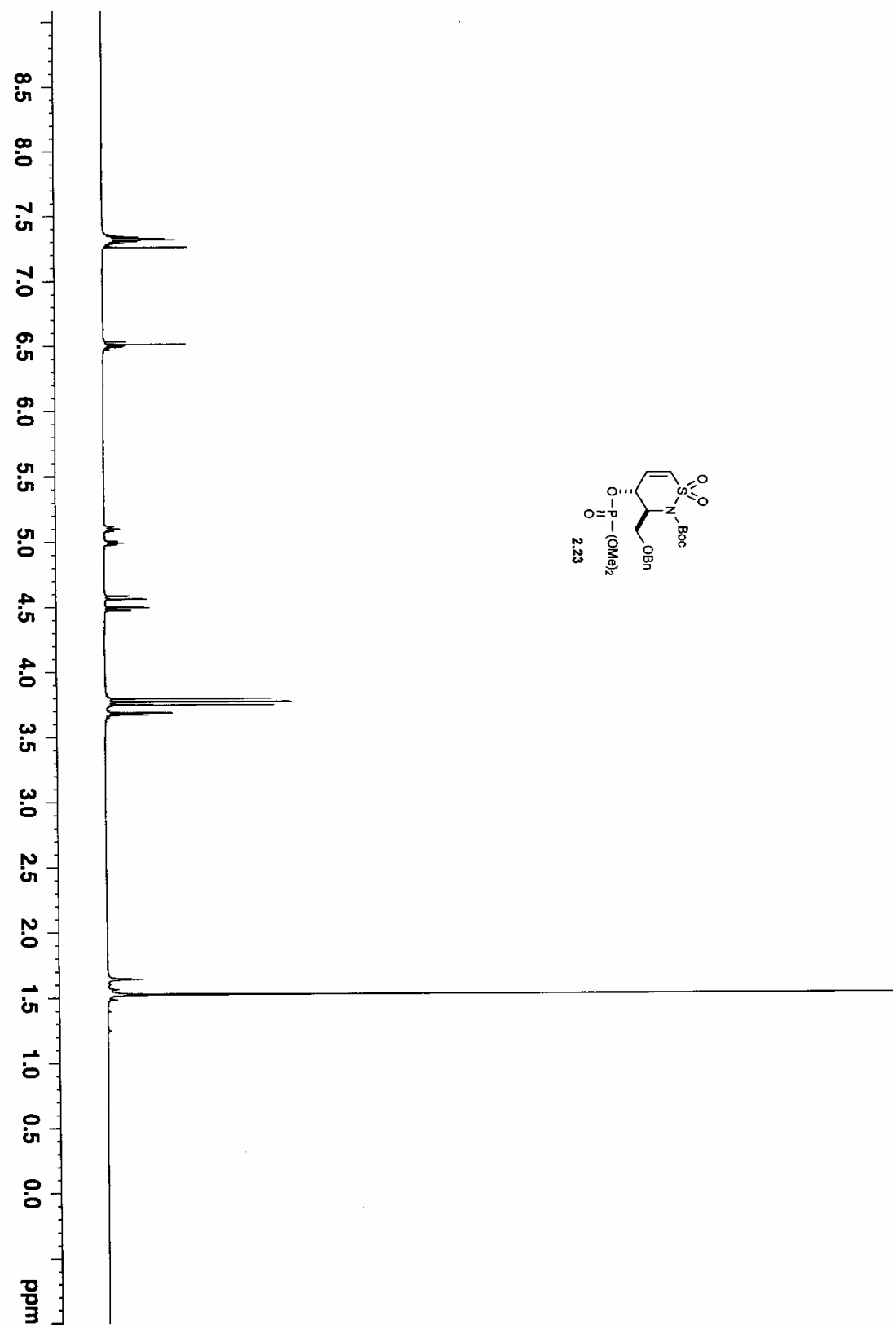
O
O
S
N
H
OBoc
OBn
2.22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6.0
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5.0
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4.0
3.5
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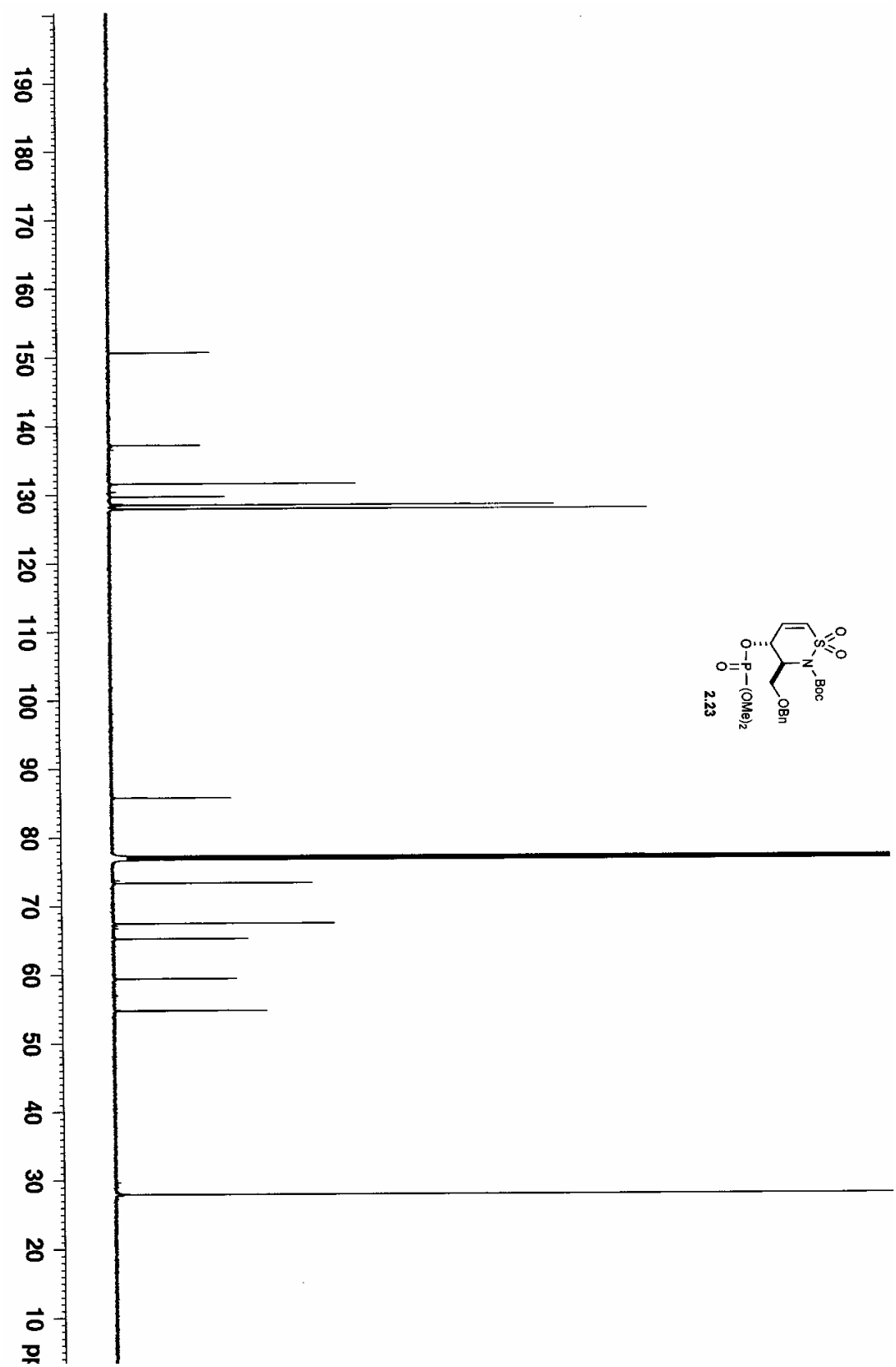
1.0
0.5
0.0
ppm
Boc
OBn
O–P–(OMe)2
2.23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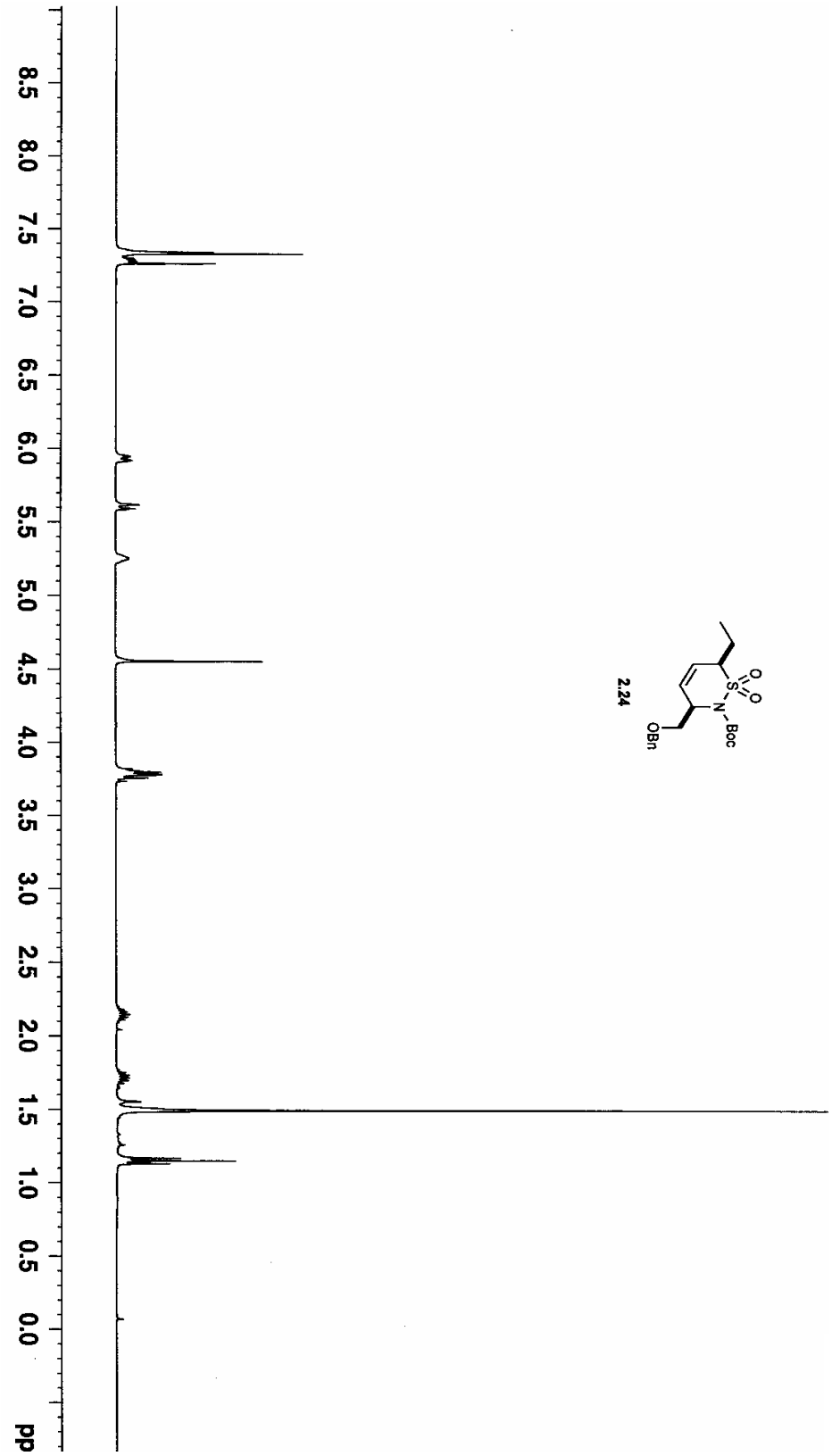
40
30
20
10
Boc
OBn
(OMe)2
2.23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4.5
4.0
3.5
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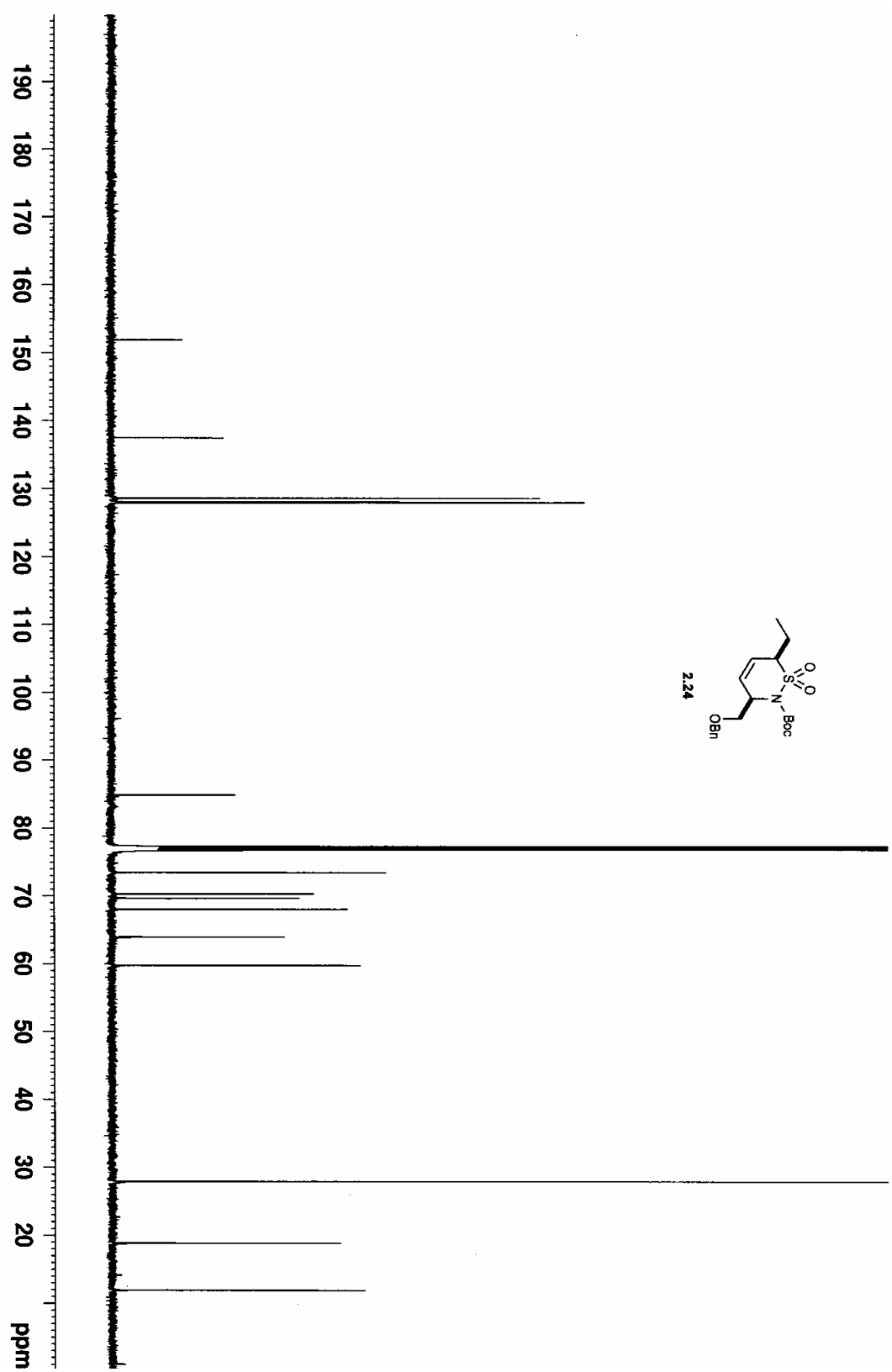
1.5
1.0
0.5
0.0
pp
O
O
S
N
Boc
OBn
2.24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90
80
70
60
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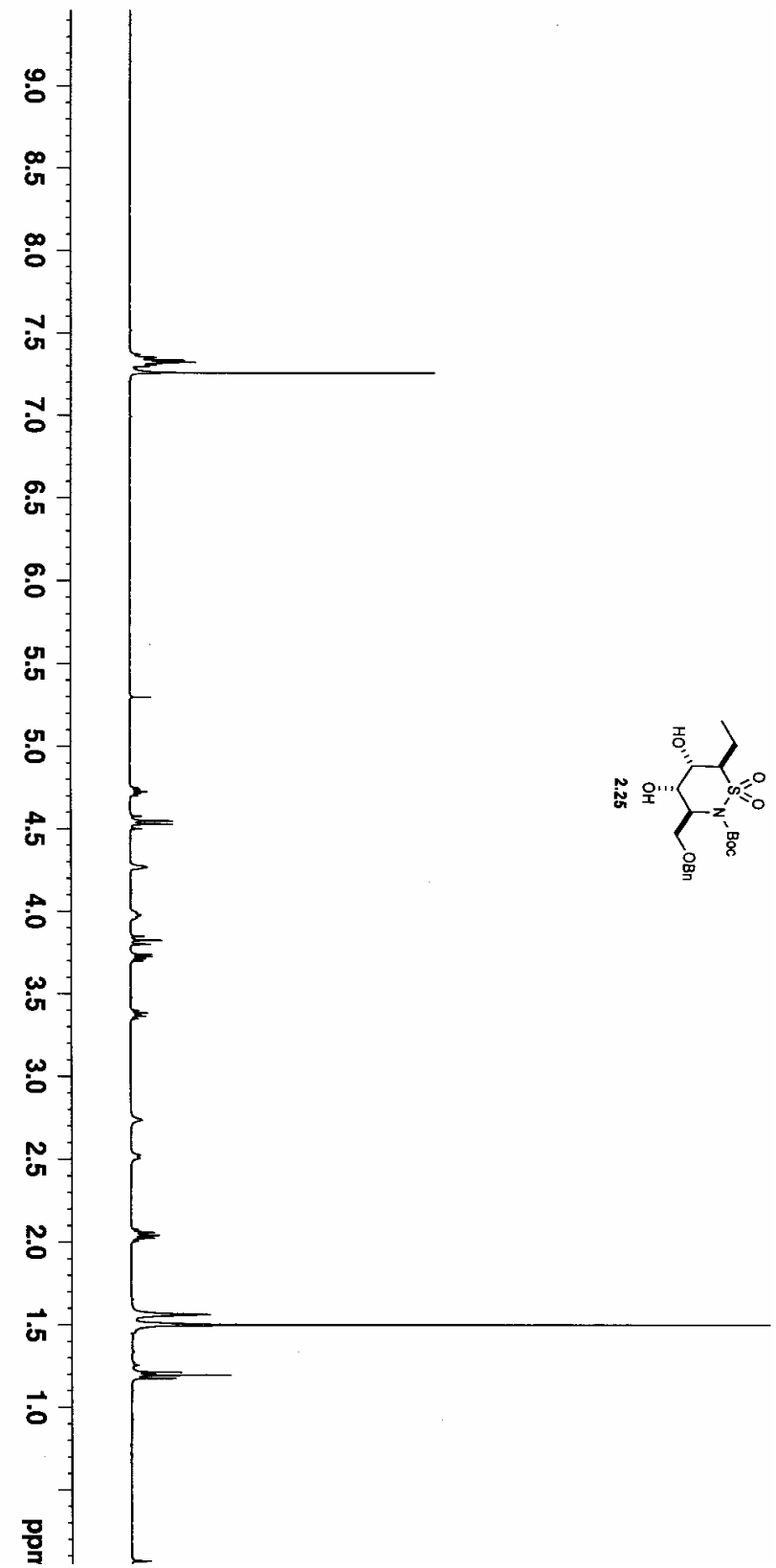
40
30
20
ppm
2.24
OBn
Boc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4.5
4.0
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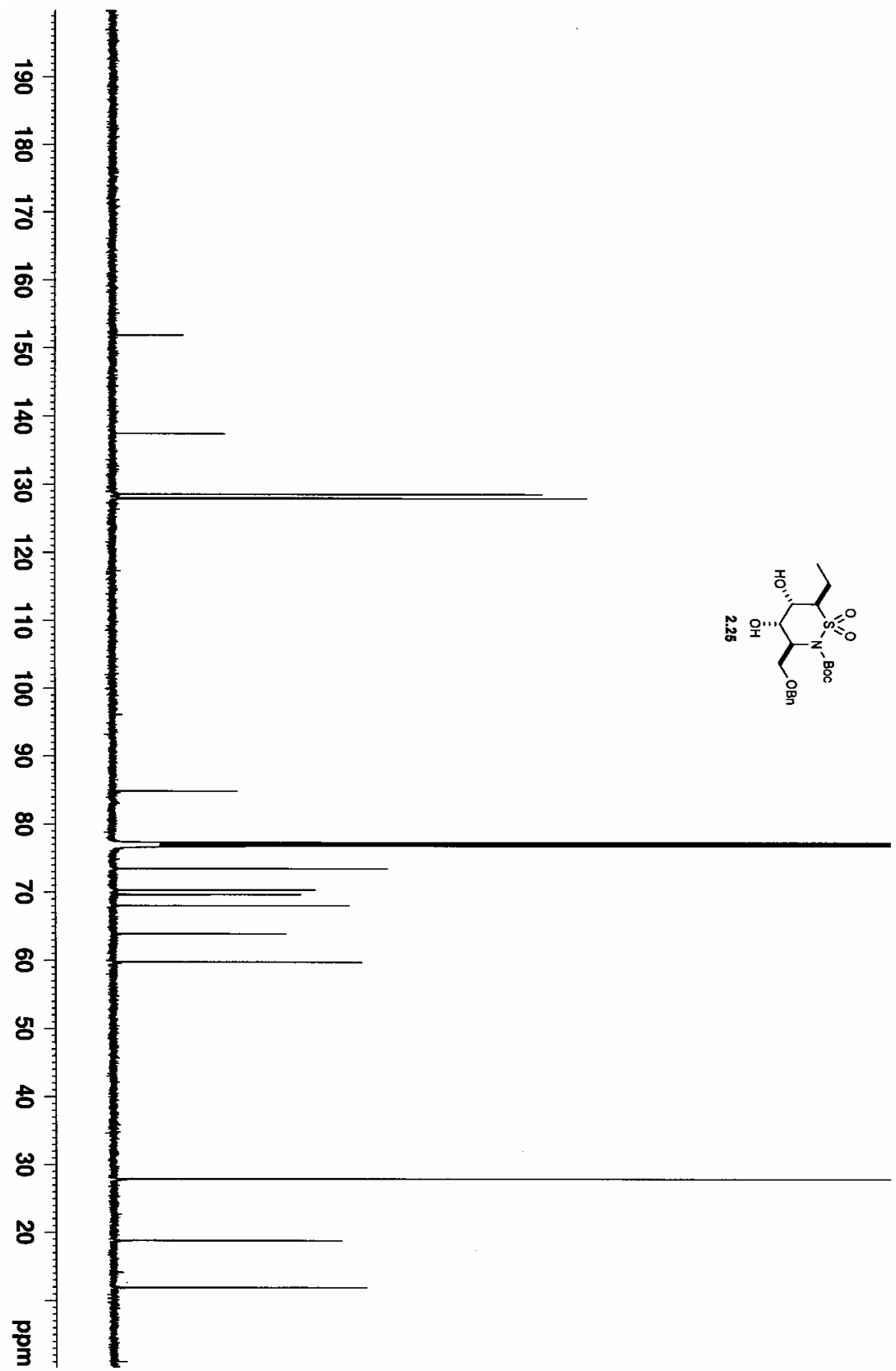
1.5
1.0
ppm
HO
OH
O
O
S
N
Boc
OBn
2.25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160
150
140
130
120
110
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60
50
40
30
20
ppm
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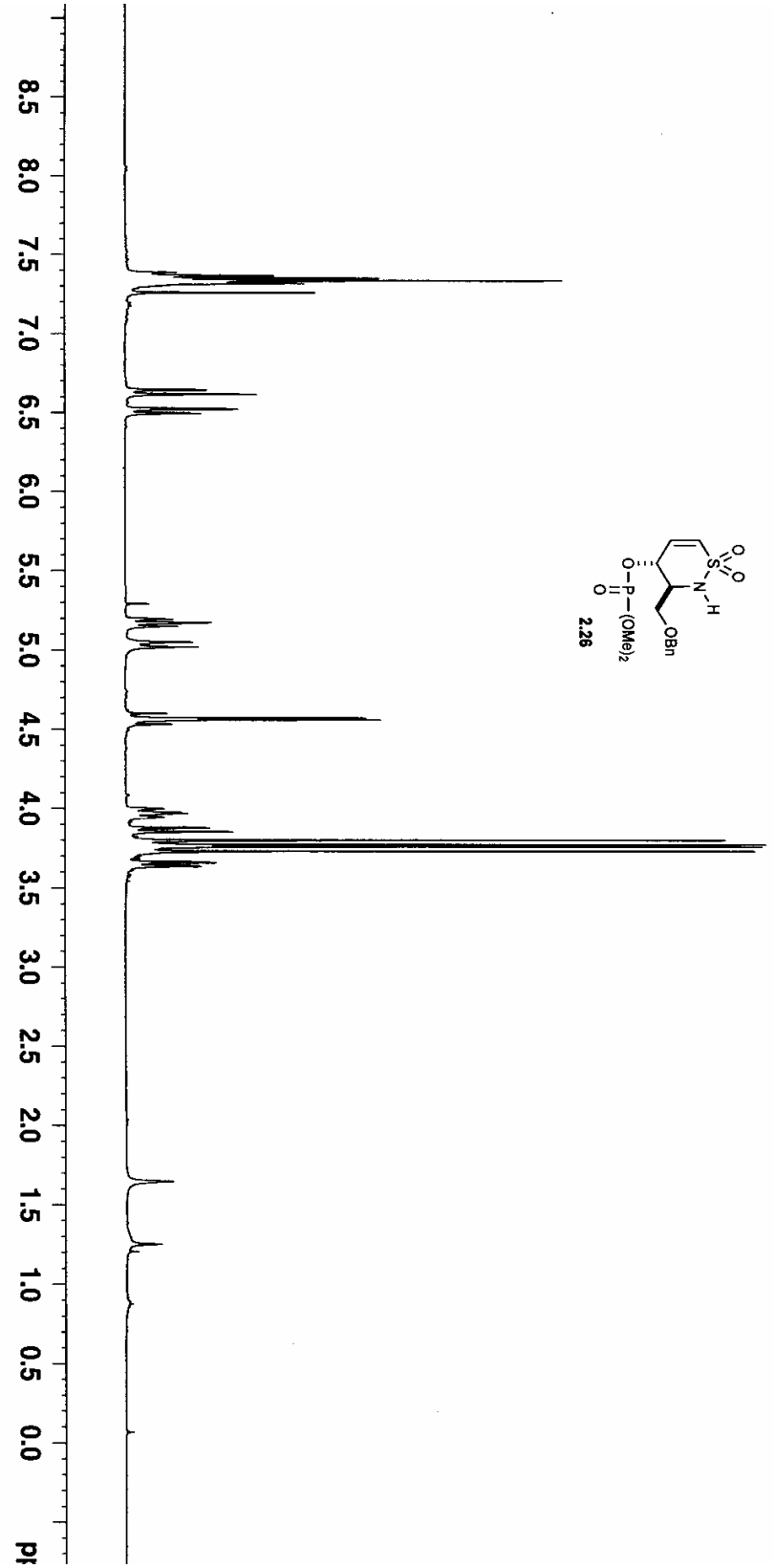
OH
S
O
O
N
Boc
OBn
2.25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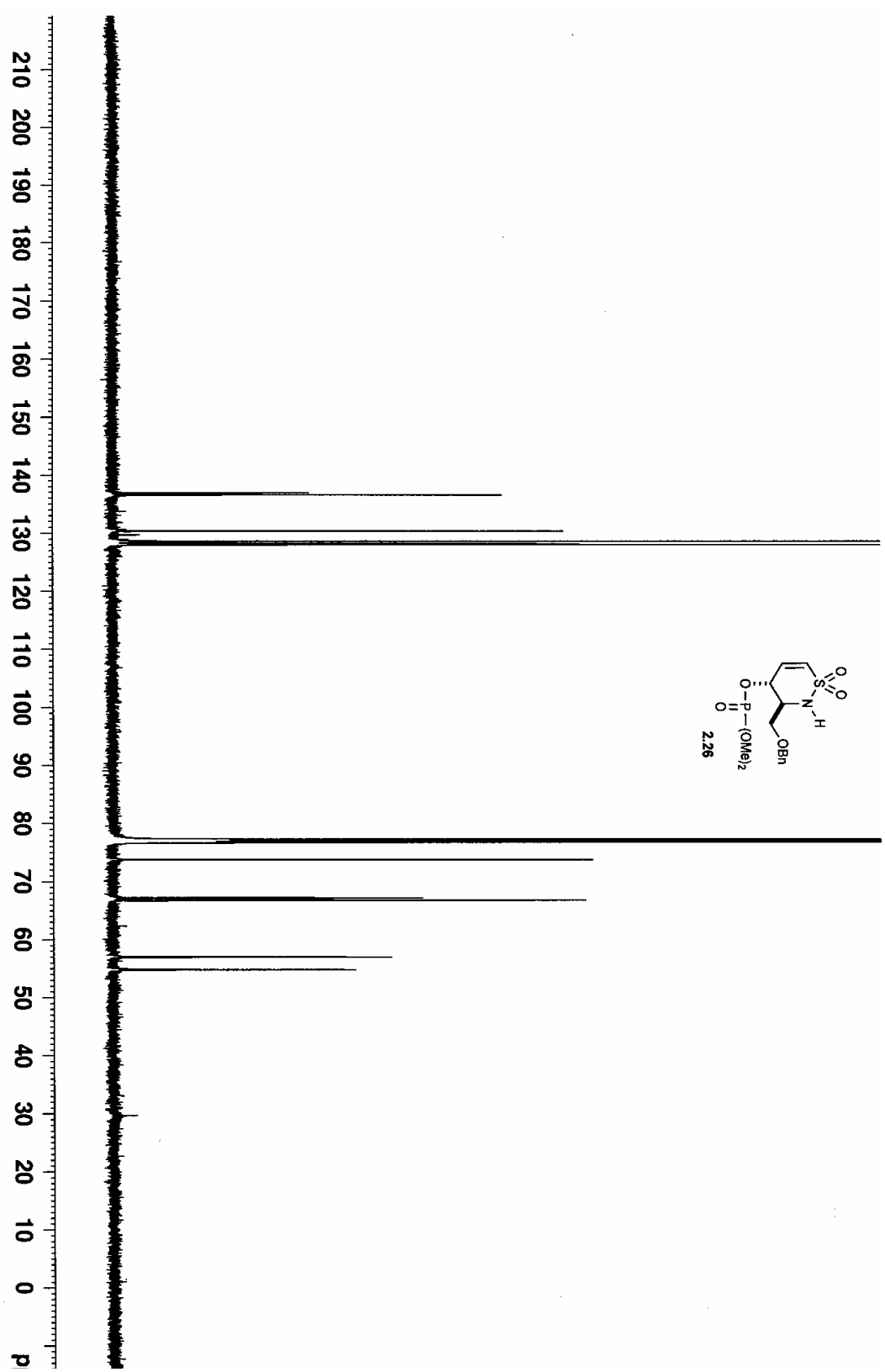
O–P–(OMe)2
2.26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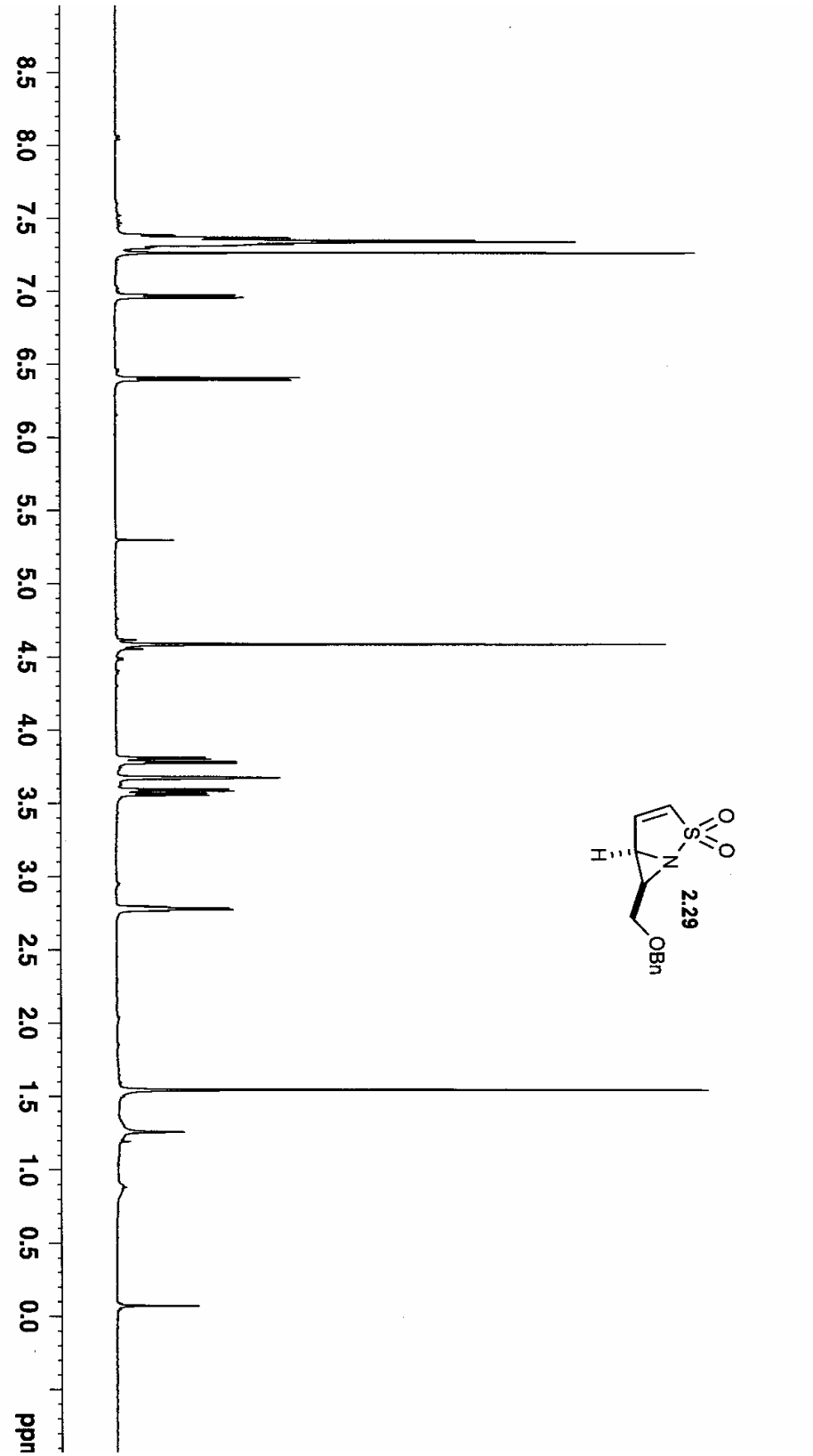
O–P–(OMe)2
2.26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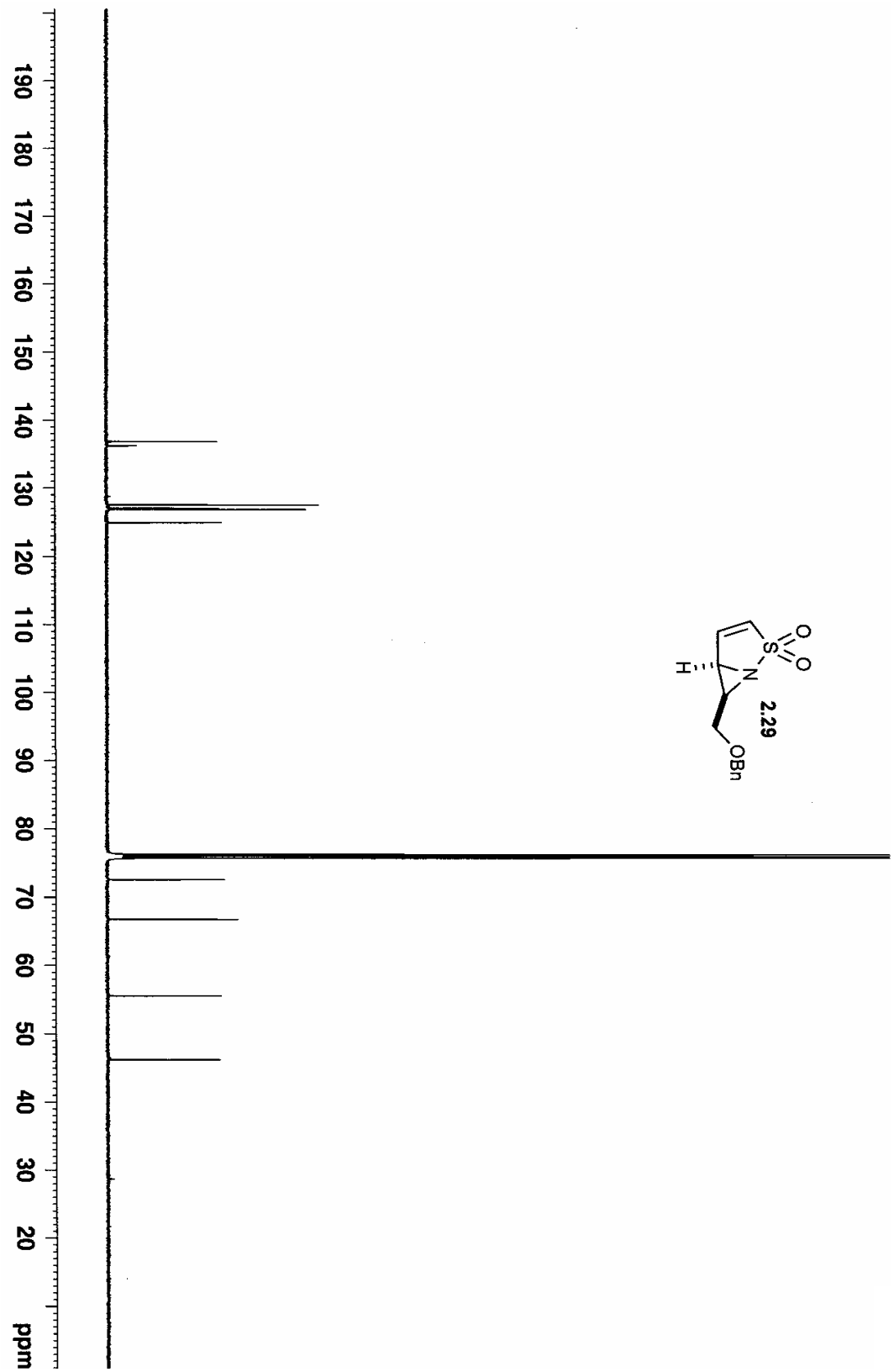
ppm
O
O
S
N
H
2.29
OBn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40
30
20
ppm
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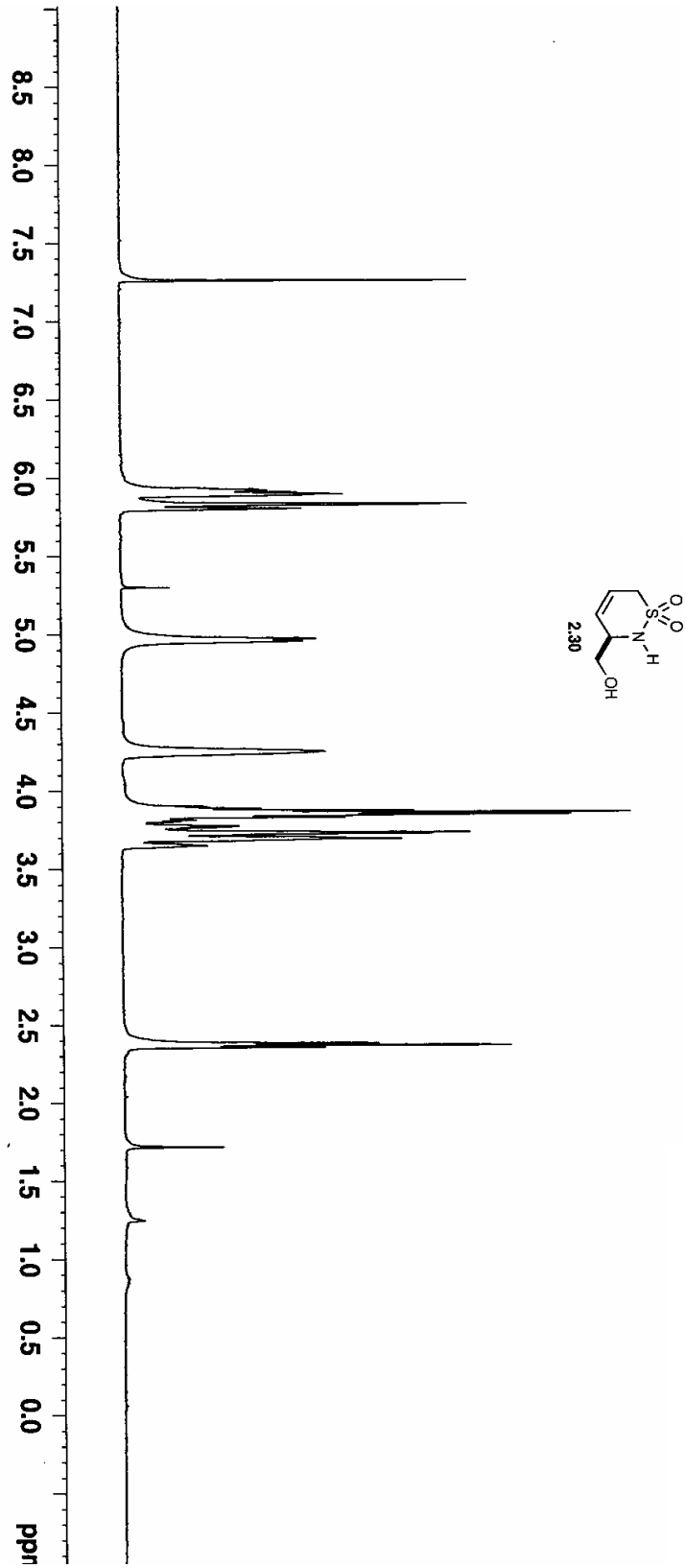
O
S
N
H
2.29
OBn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1.0
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ppm
2.30
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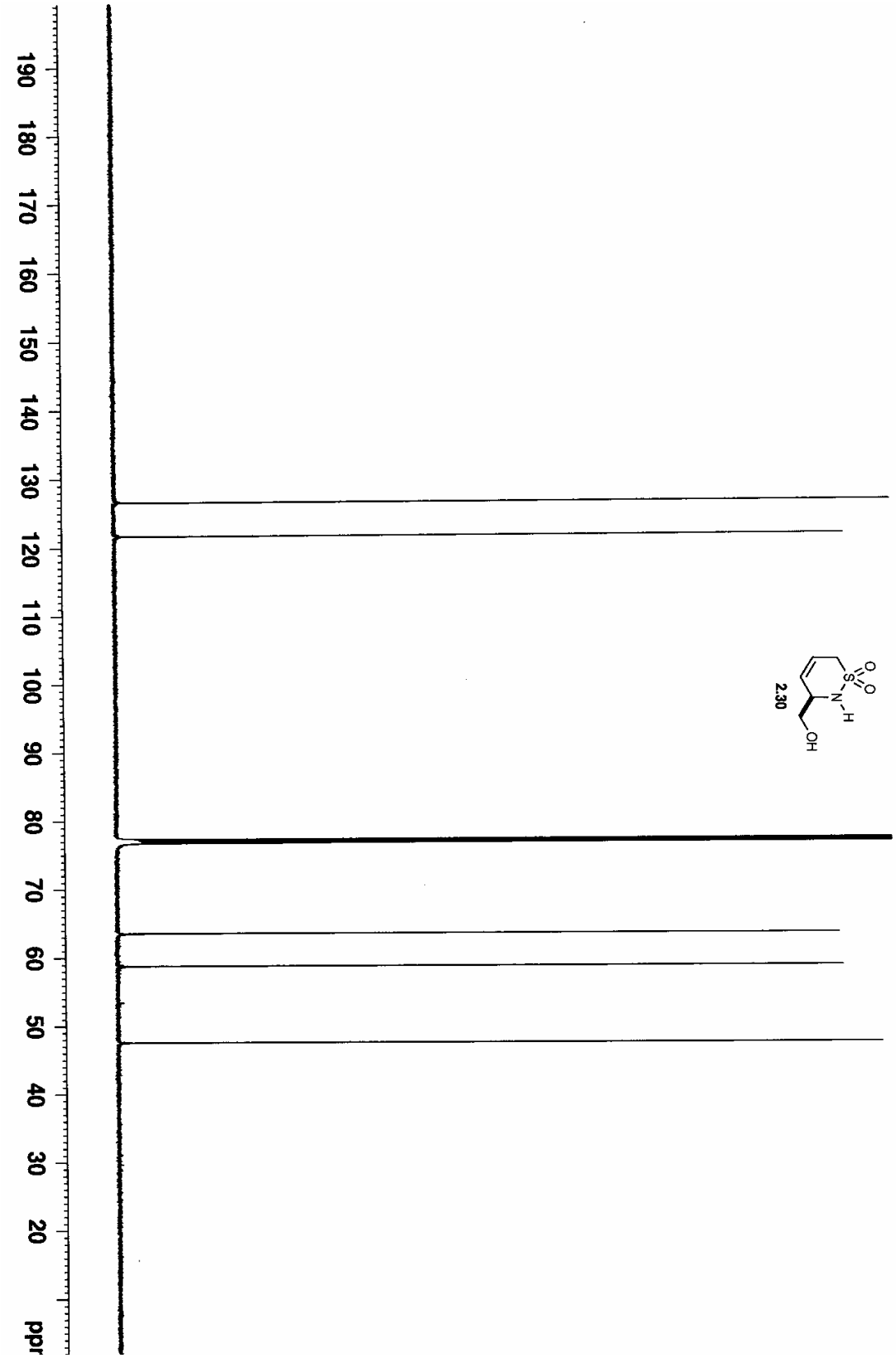
O
S
N
H
OH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40
30
20
ppr
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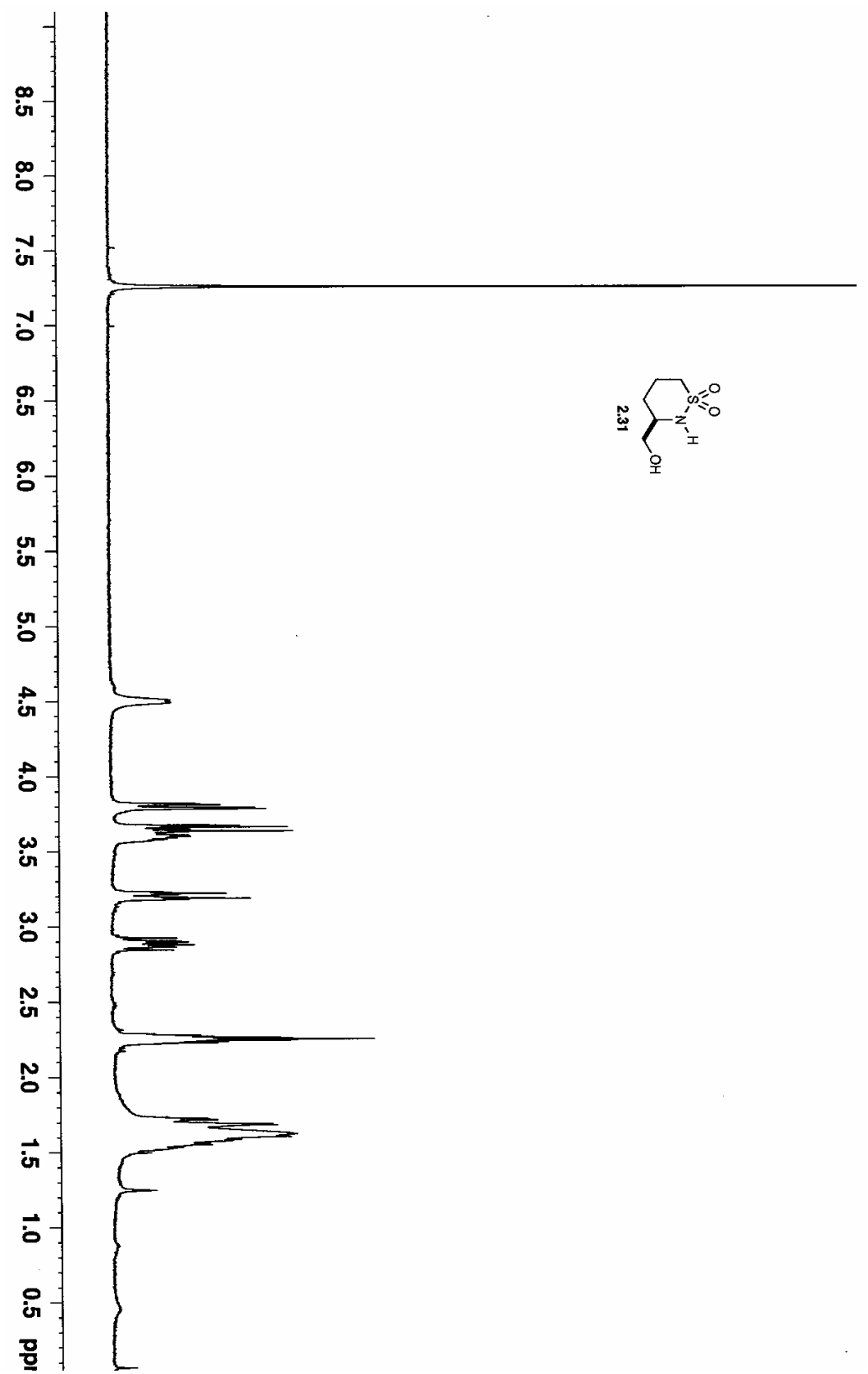
S
N
H
OH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4.0
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1.5
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0.5
ppm
2.31
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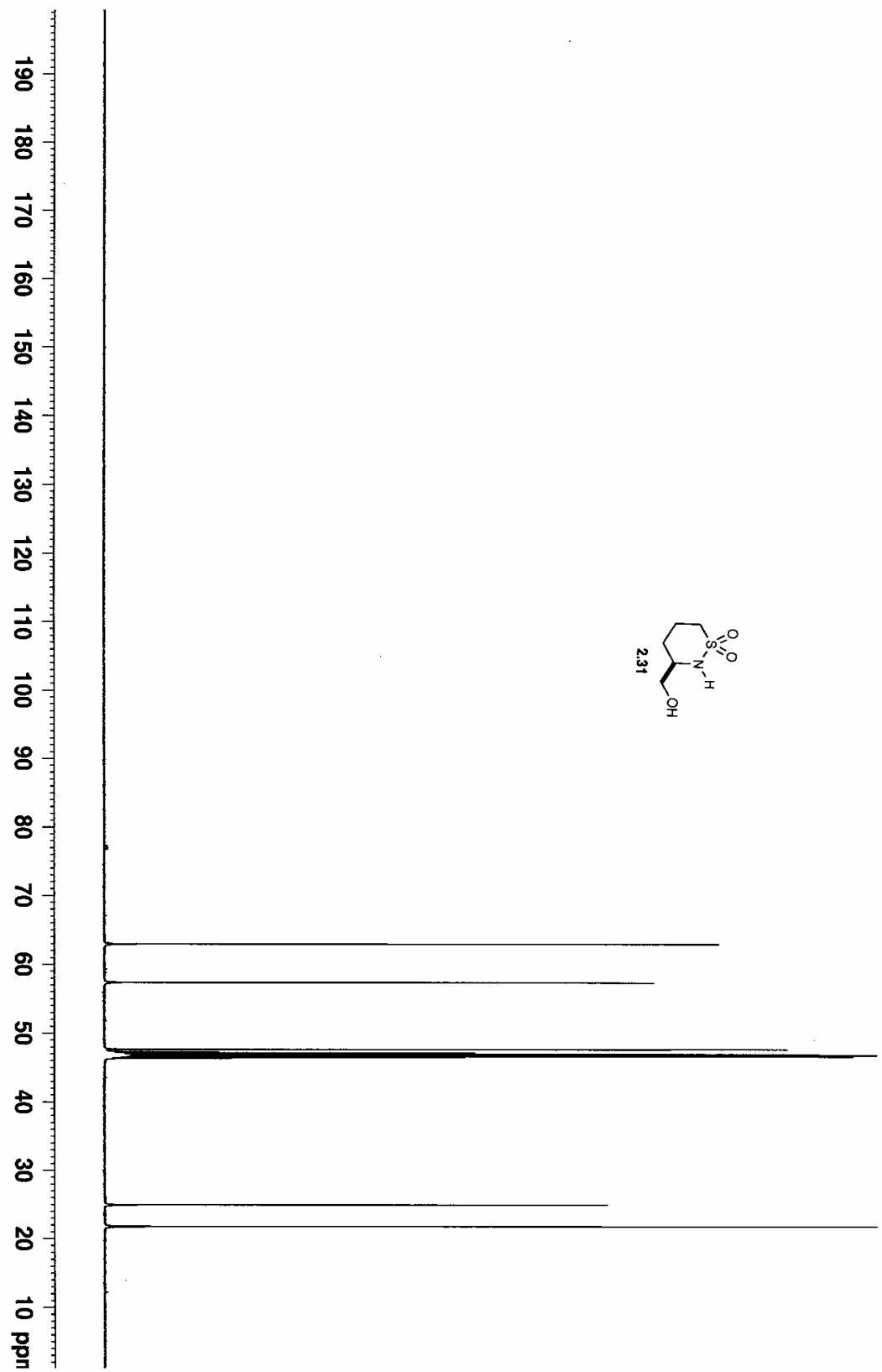
O
S
N
H
OH


190
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150
140
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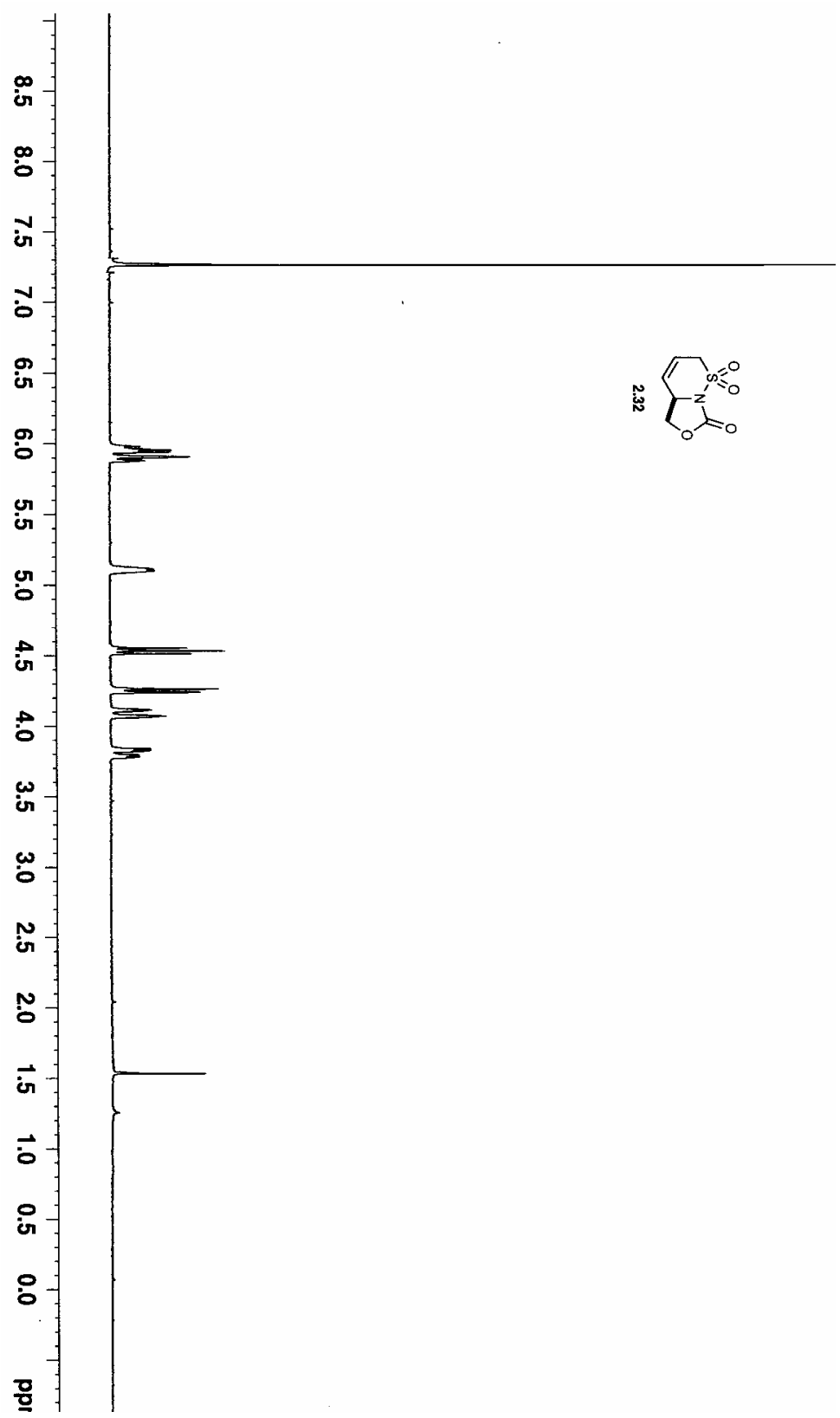
70
60
50
40
30
20
10 ppm
2.31
O
O
S
N
H
OH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6.0
5.5
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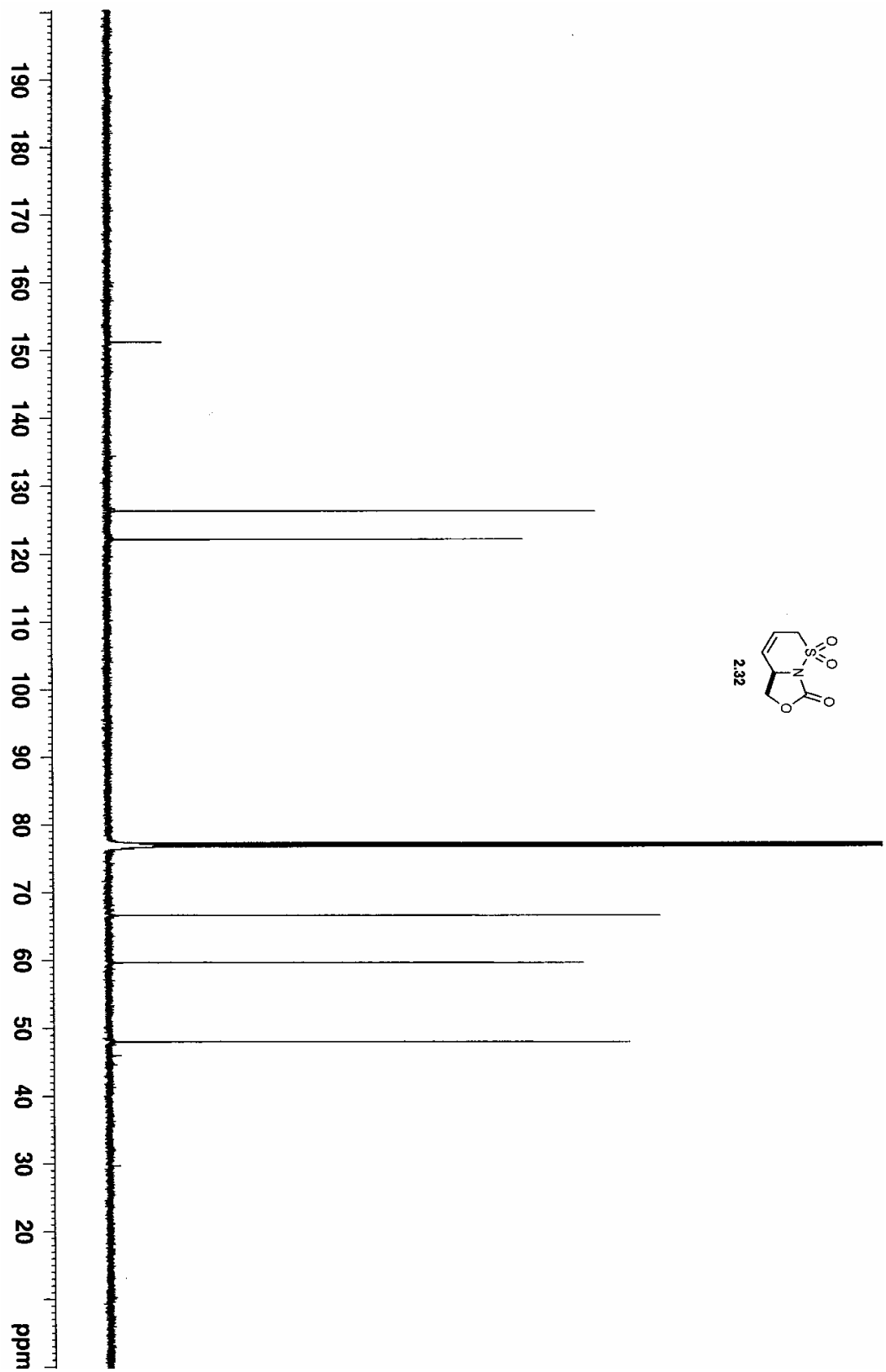
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.32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100
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70
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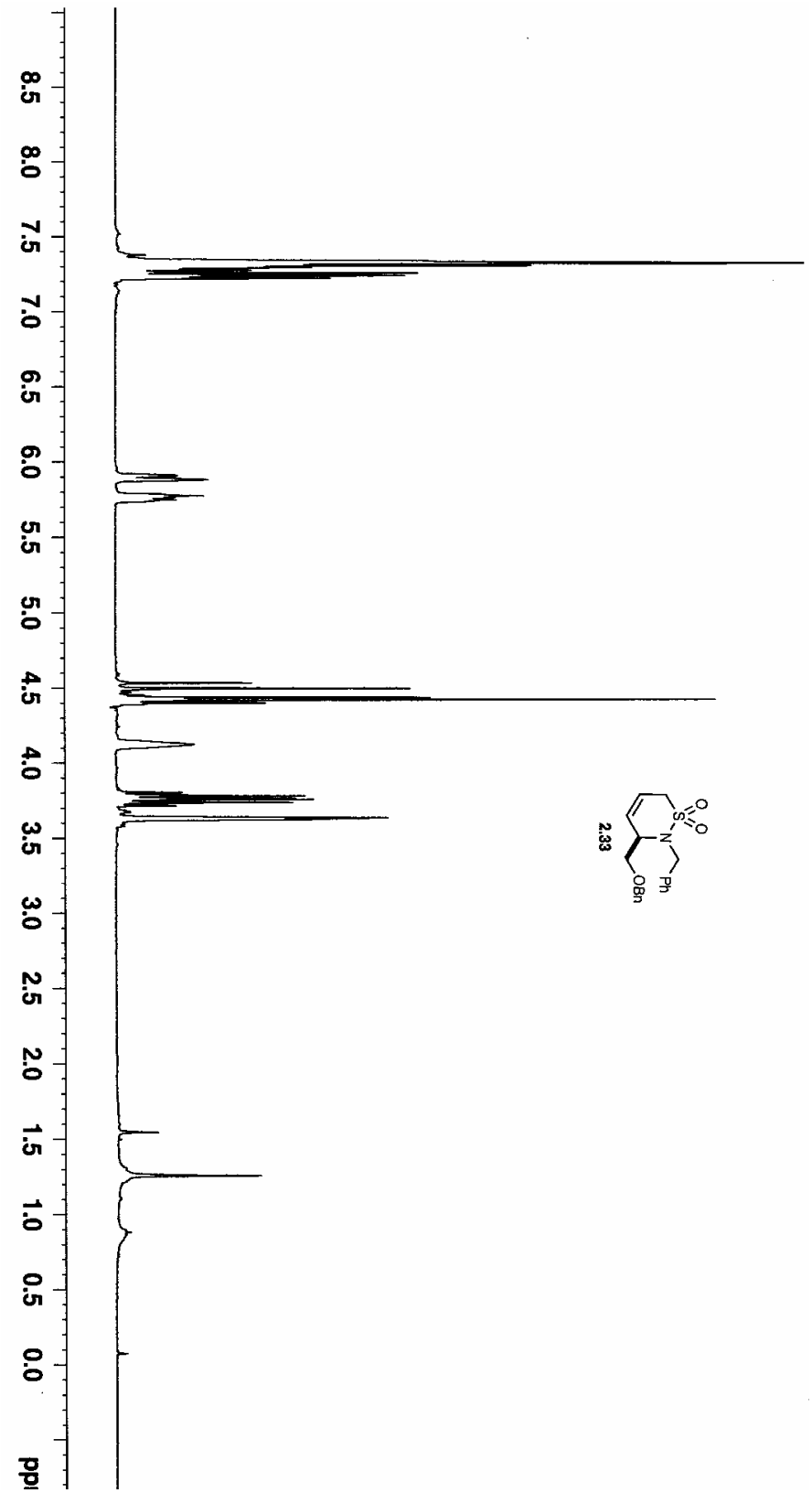
30
20
ppm
2.32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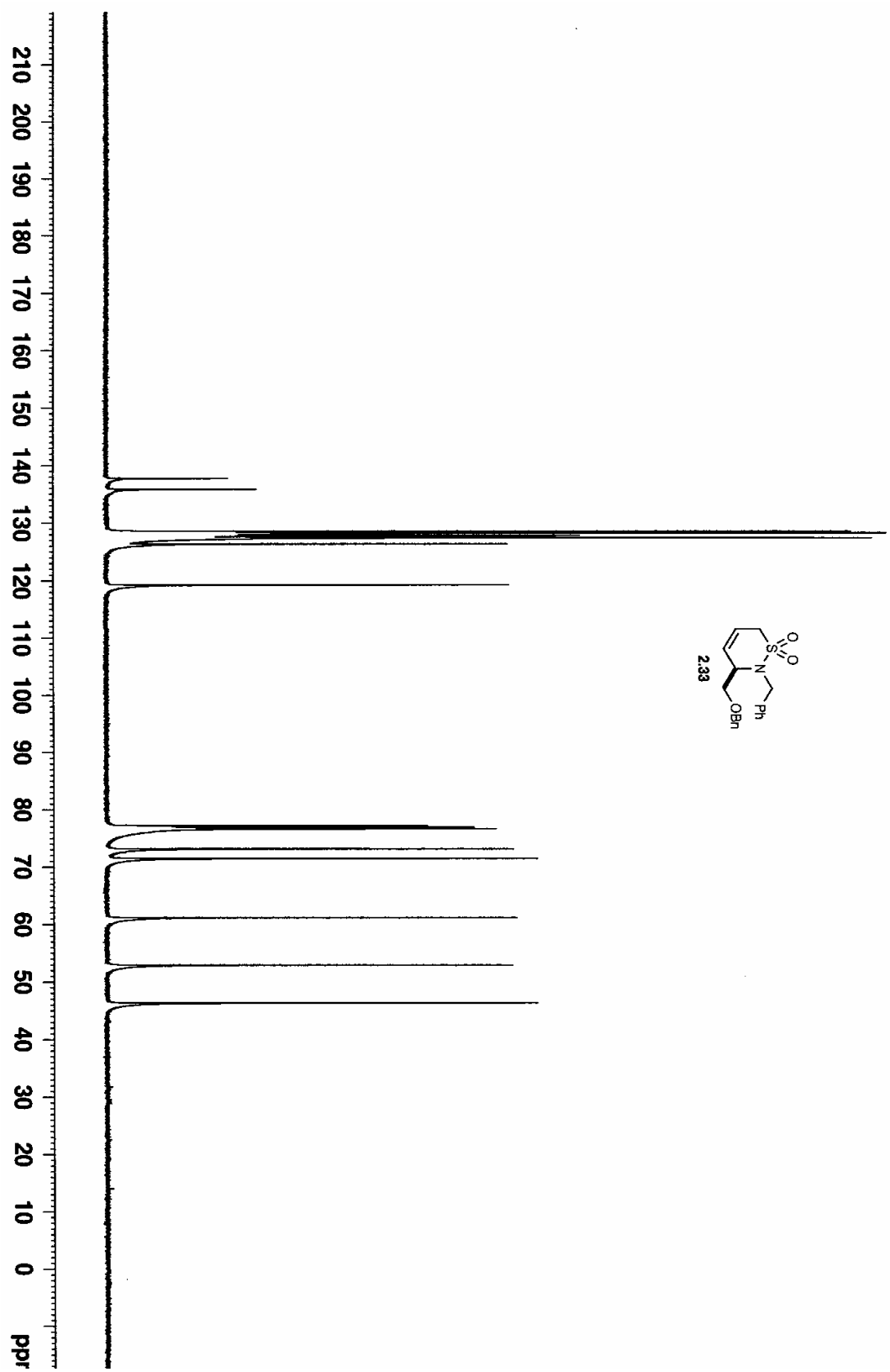
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
O
O
S
N
Ph
OBn
2.33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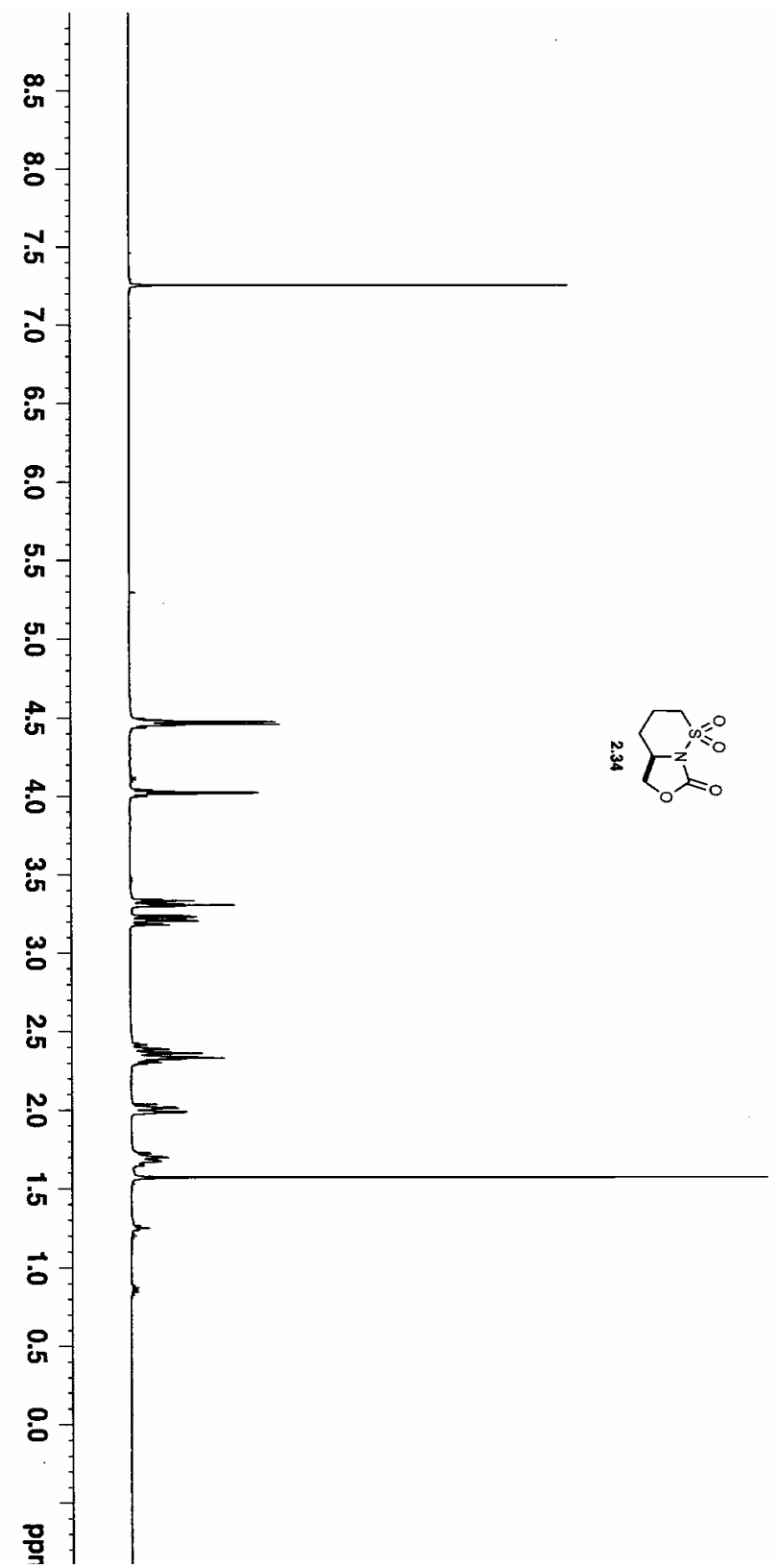
Ph
OBn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6.5
6.0
5.5
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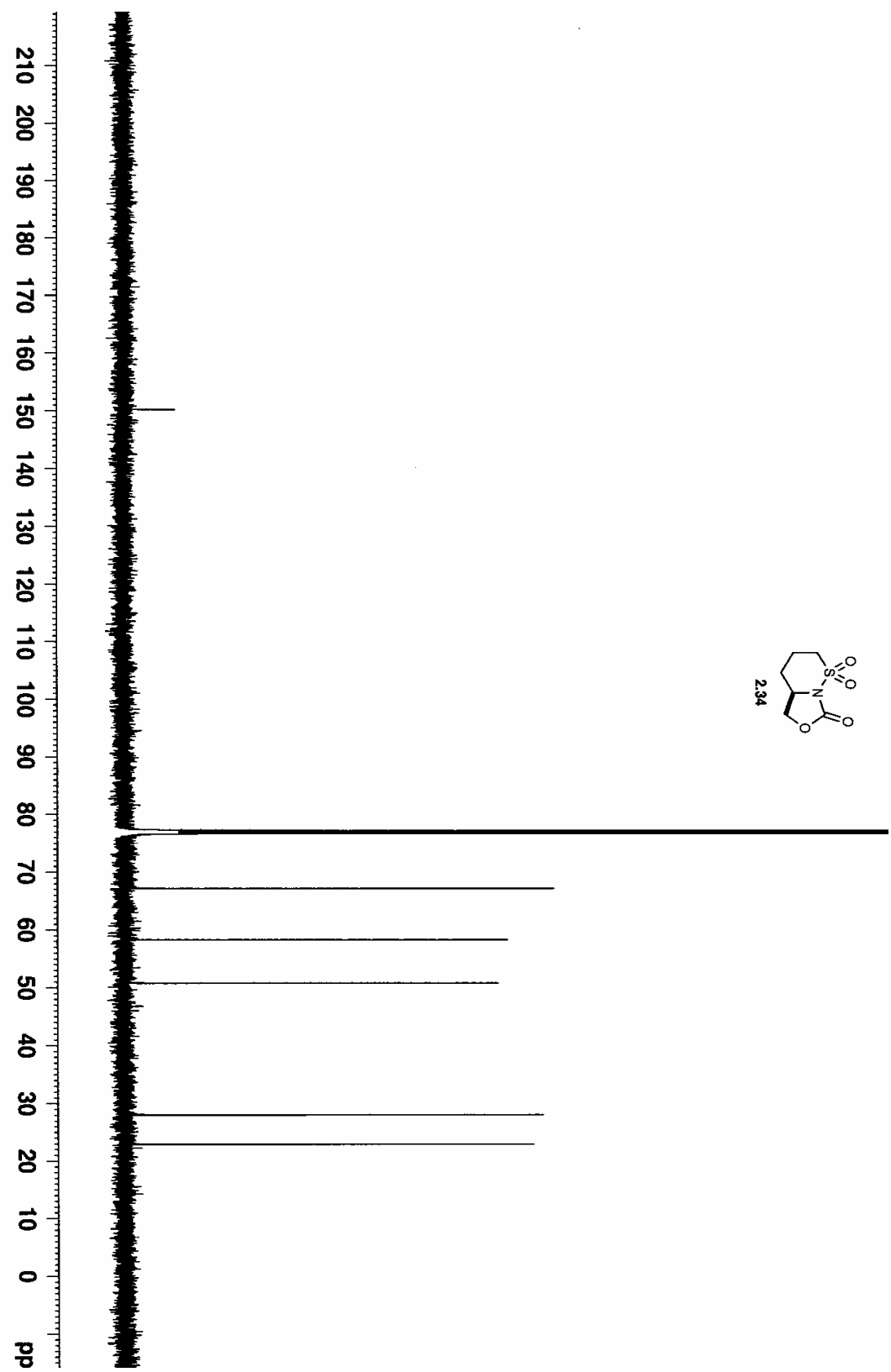
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.34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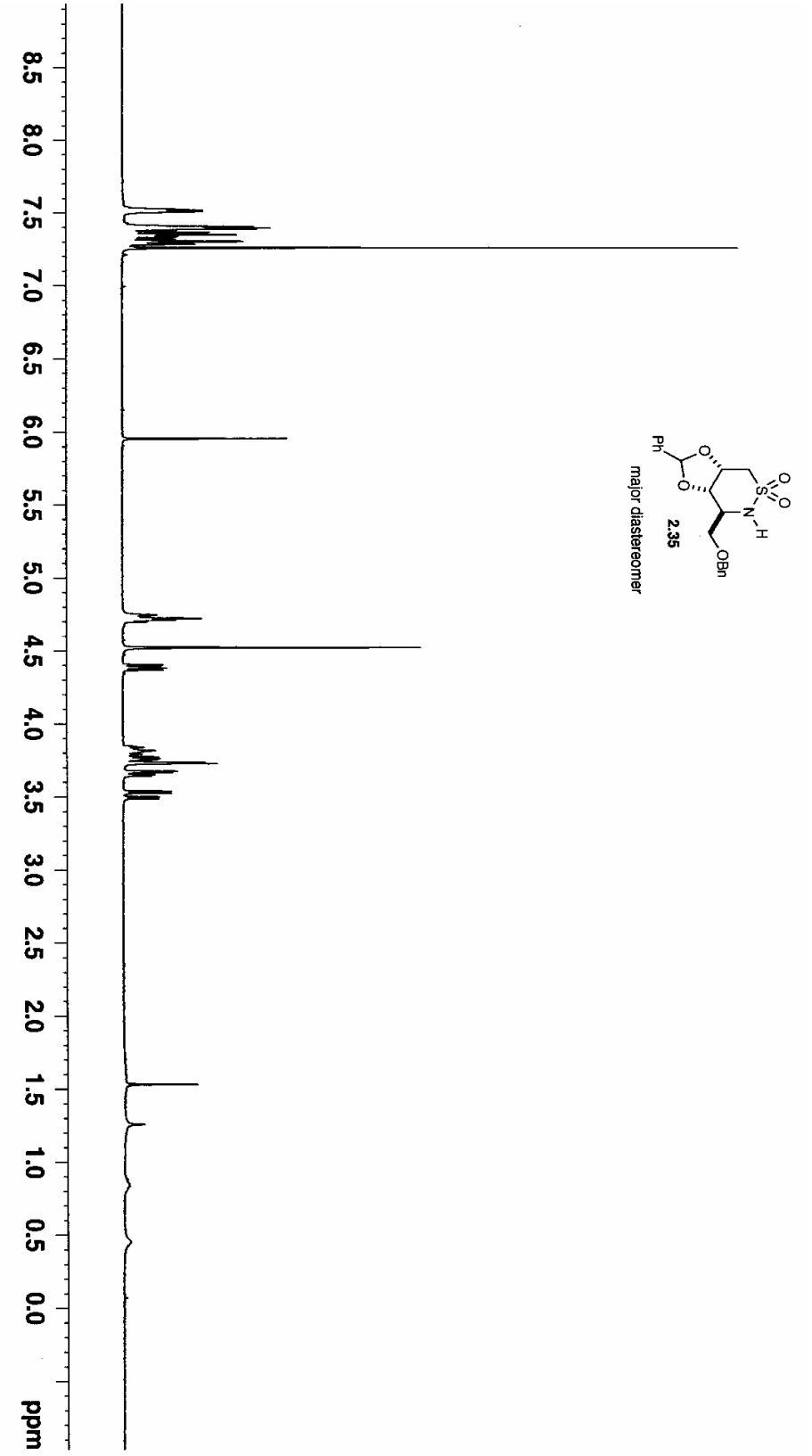
2.34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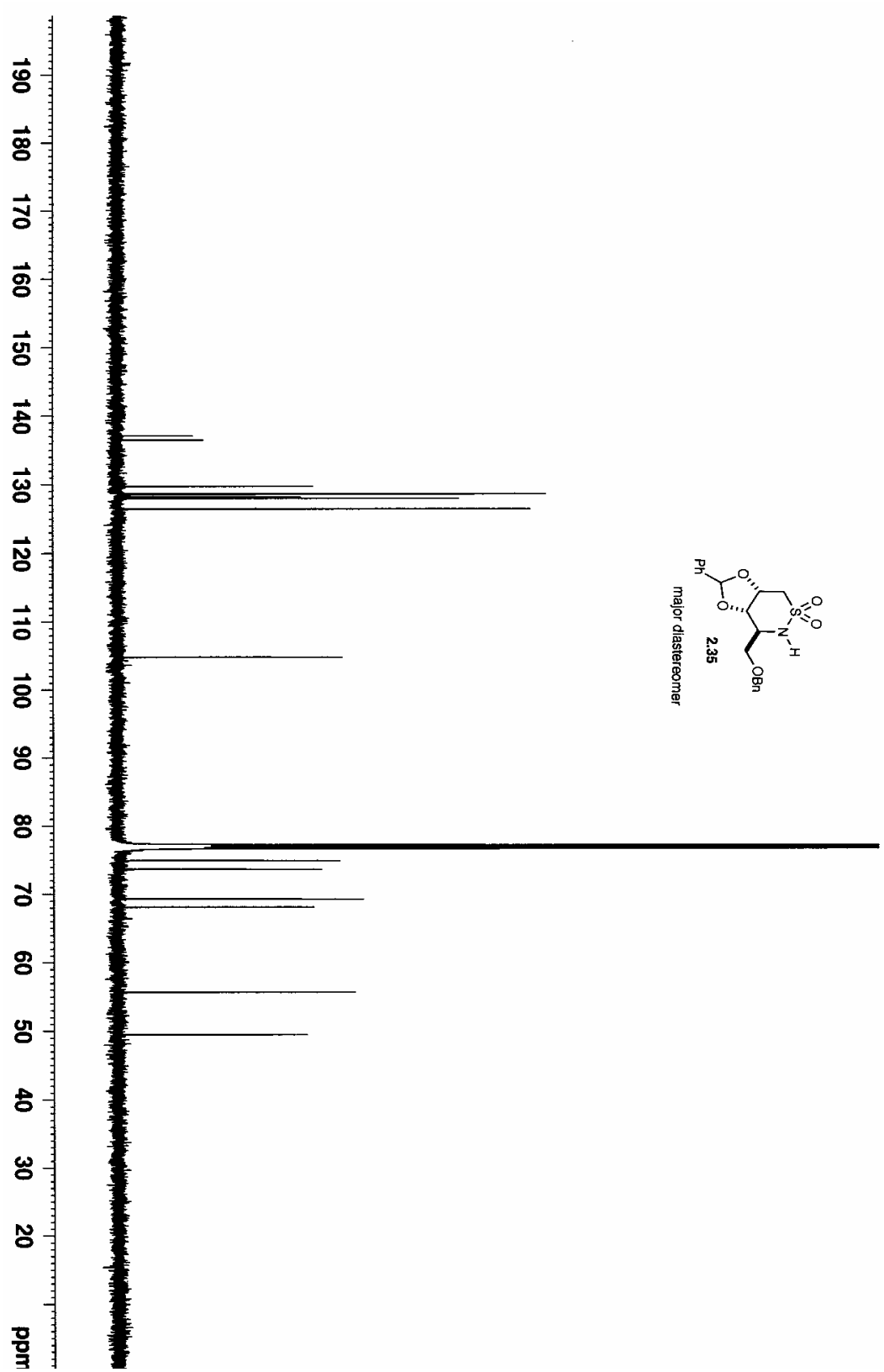
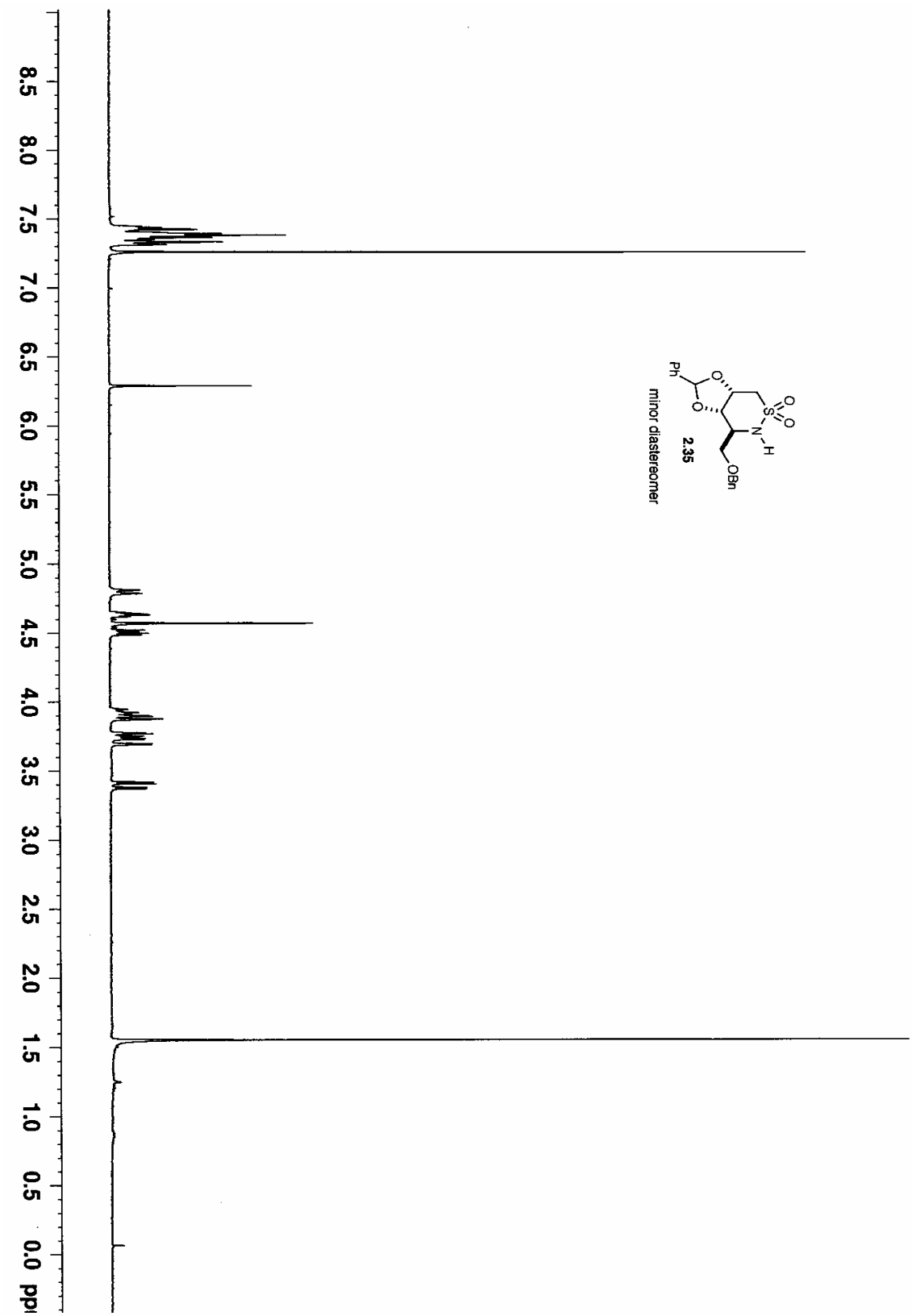
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
Ph
O
O
S
O
O
N
H
OBn
2.35
major diastereomer


major diastereomer
2.35
Ph
OBn
ppm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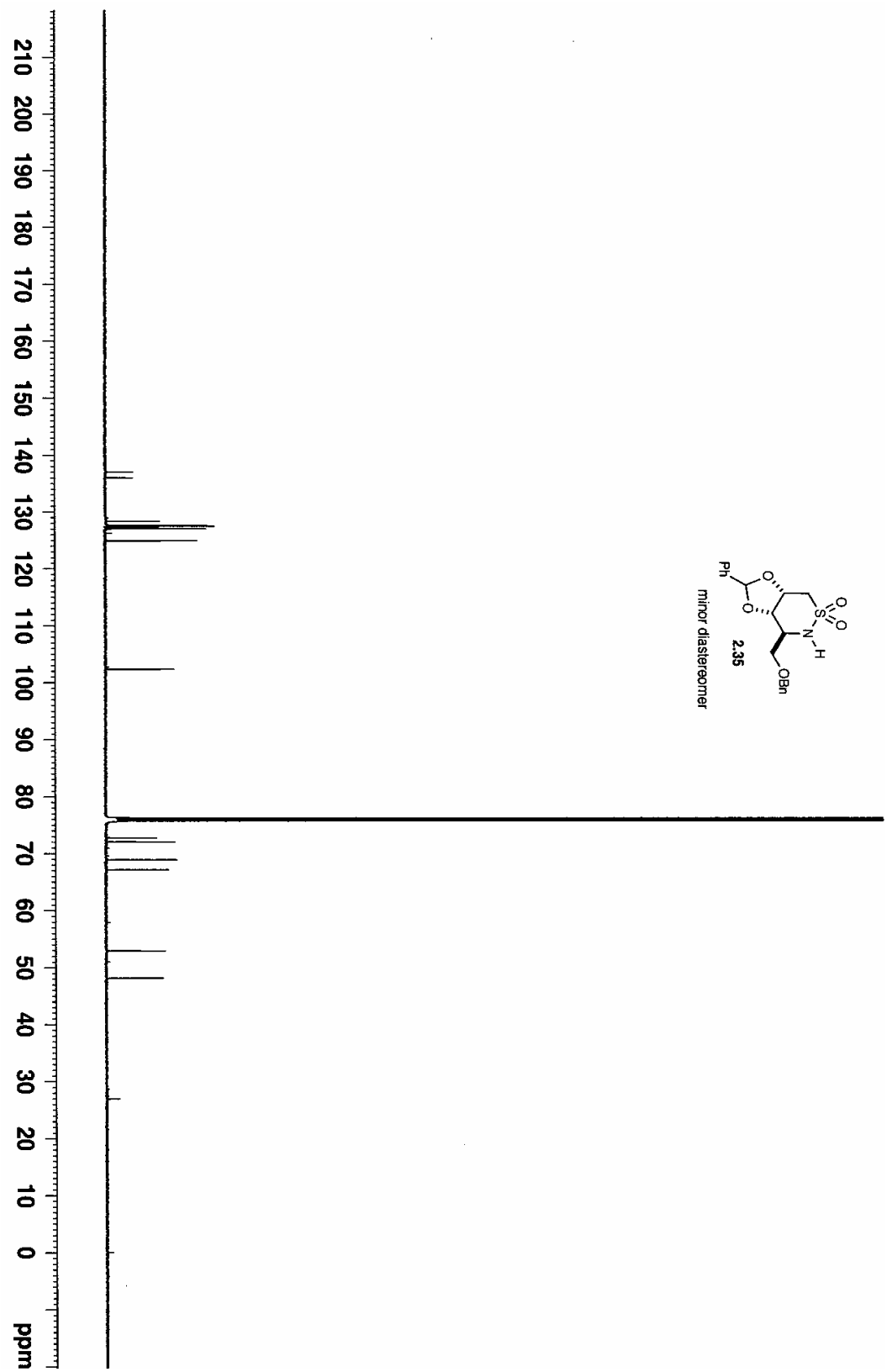
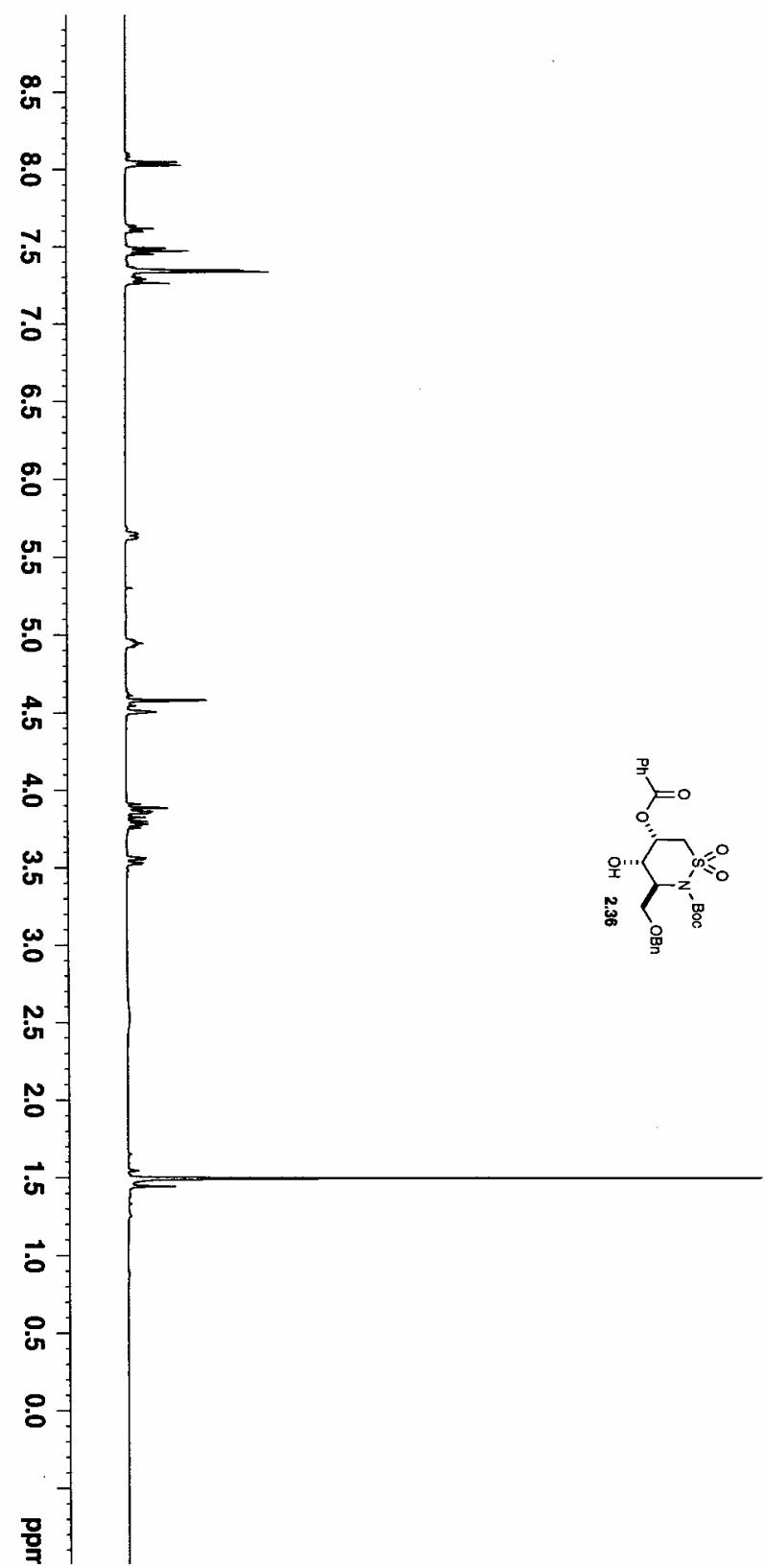
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0 ppm
Ph
O
O
O
O
S
N
H
OBn
2.35
minor diastereomer


minor diastereomer
2.35
Ph
OBn
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm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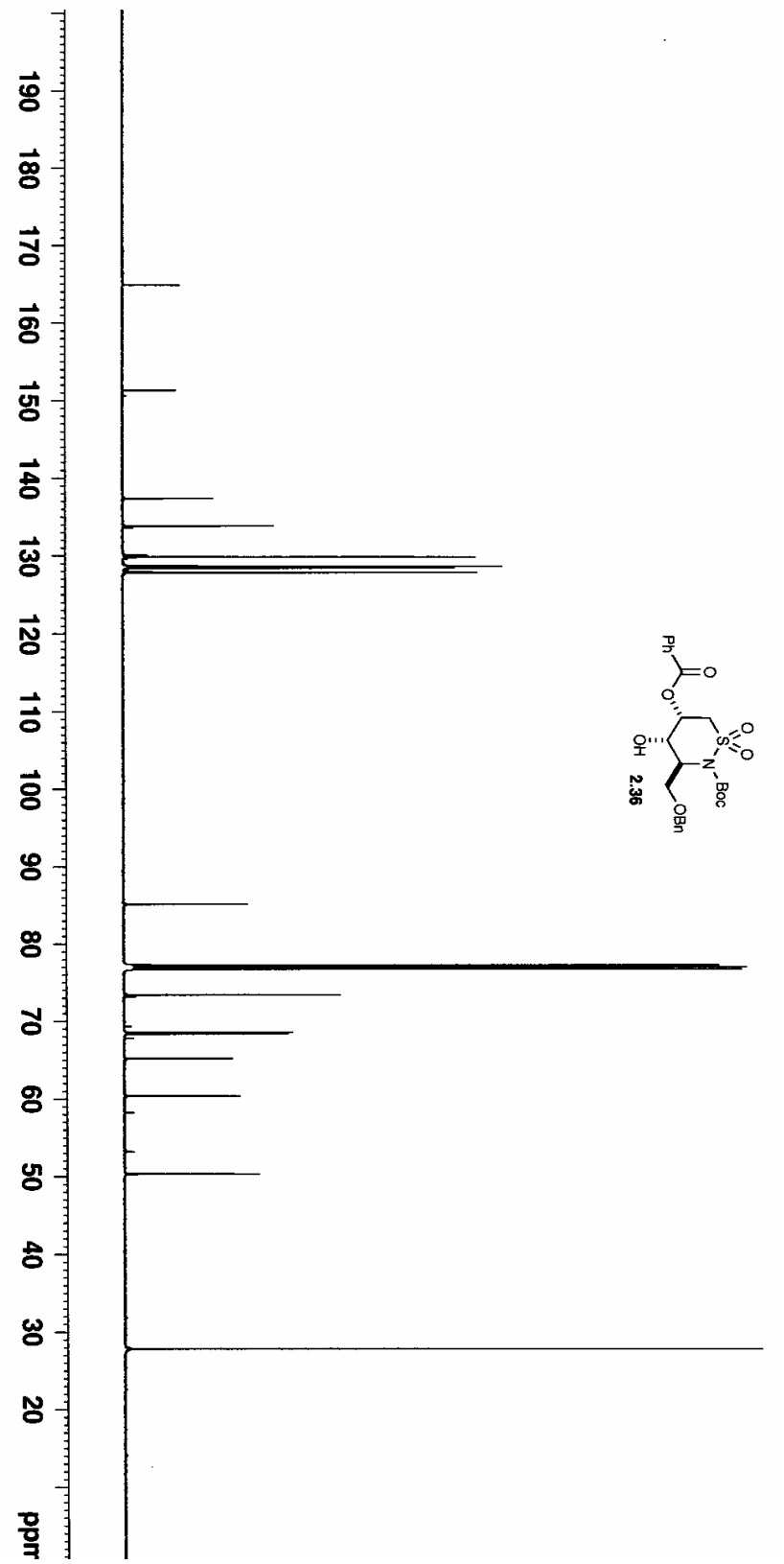
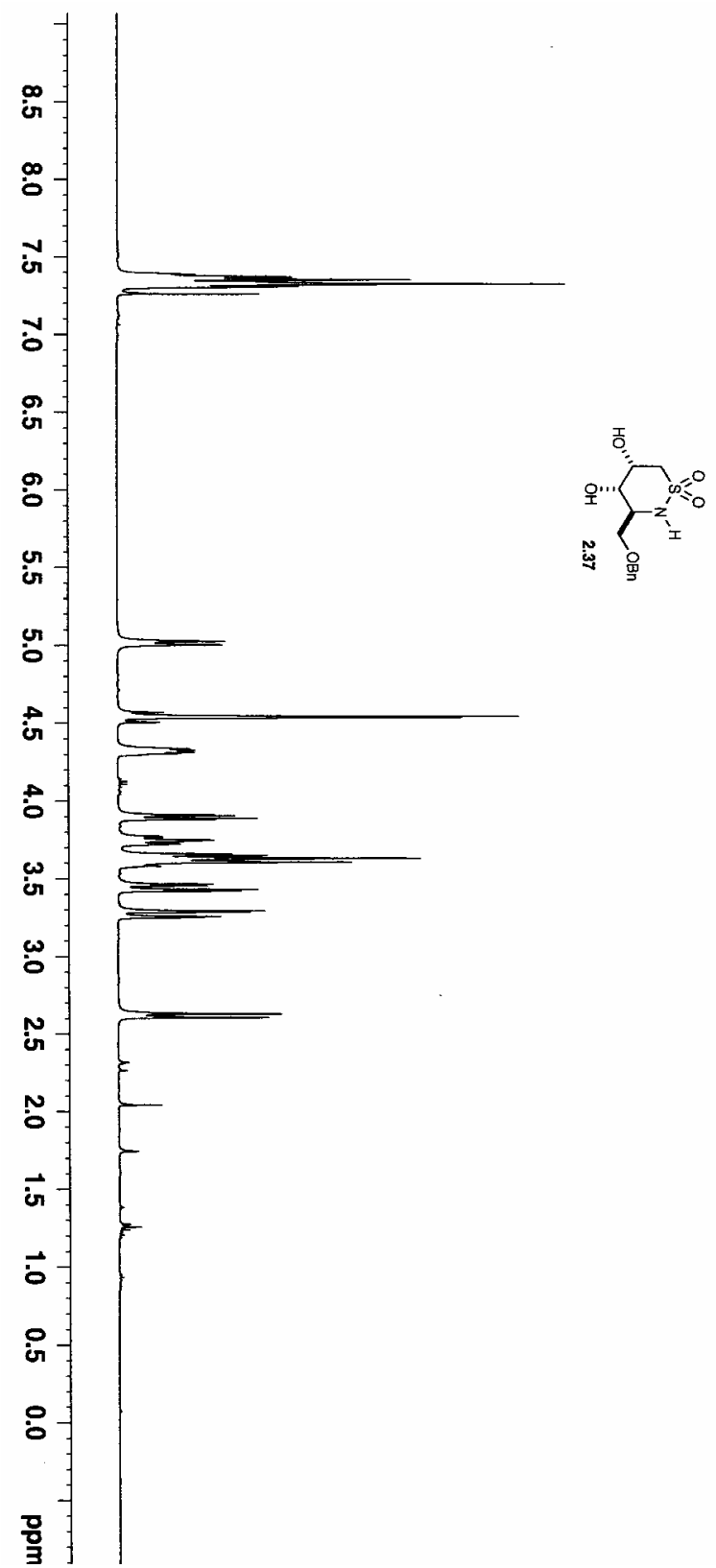
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
Ph
O
O
OH
2.36
S
O
O
N
Boc
OBn


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm
Ph
O
O
O
OH
2.36
S
O
O
N
Boc
OBn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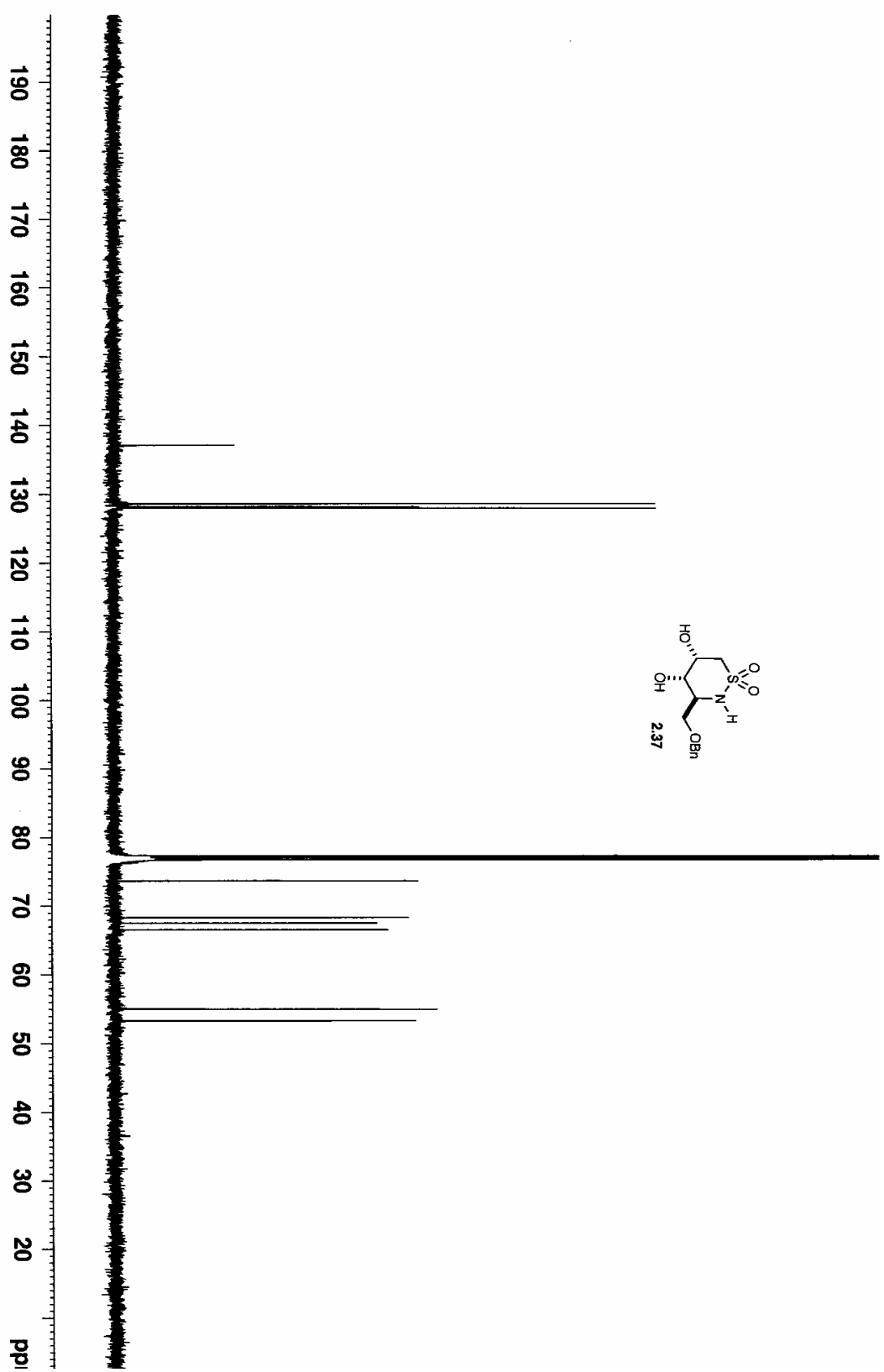
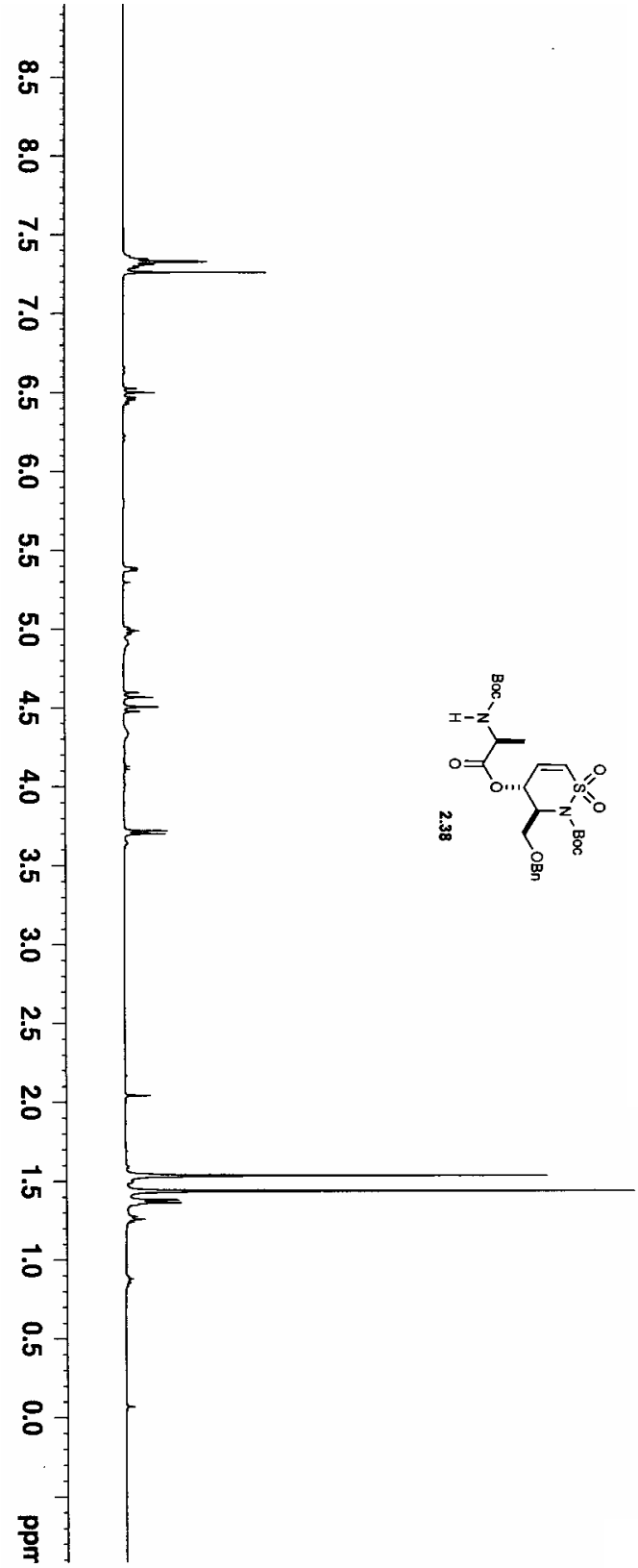
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
HO
OH
O
O
S
N
H
OBn
2.37


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppl
HO
OH
O
O
S
N
H
OBn
2.37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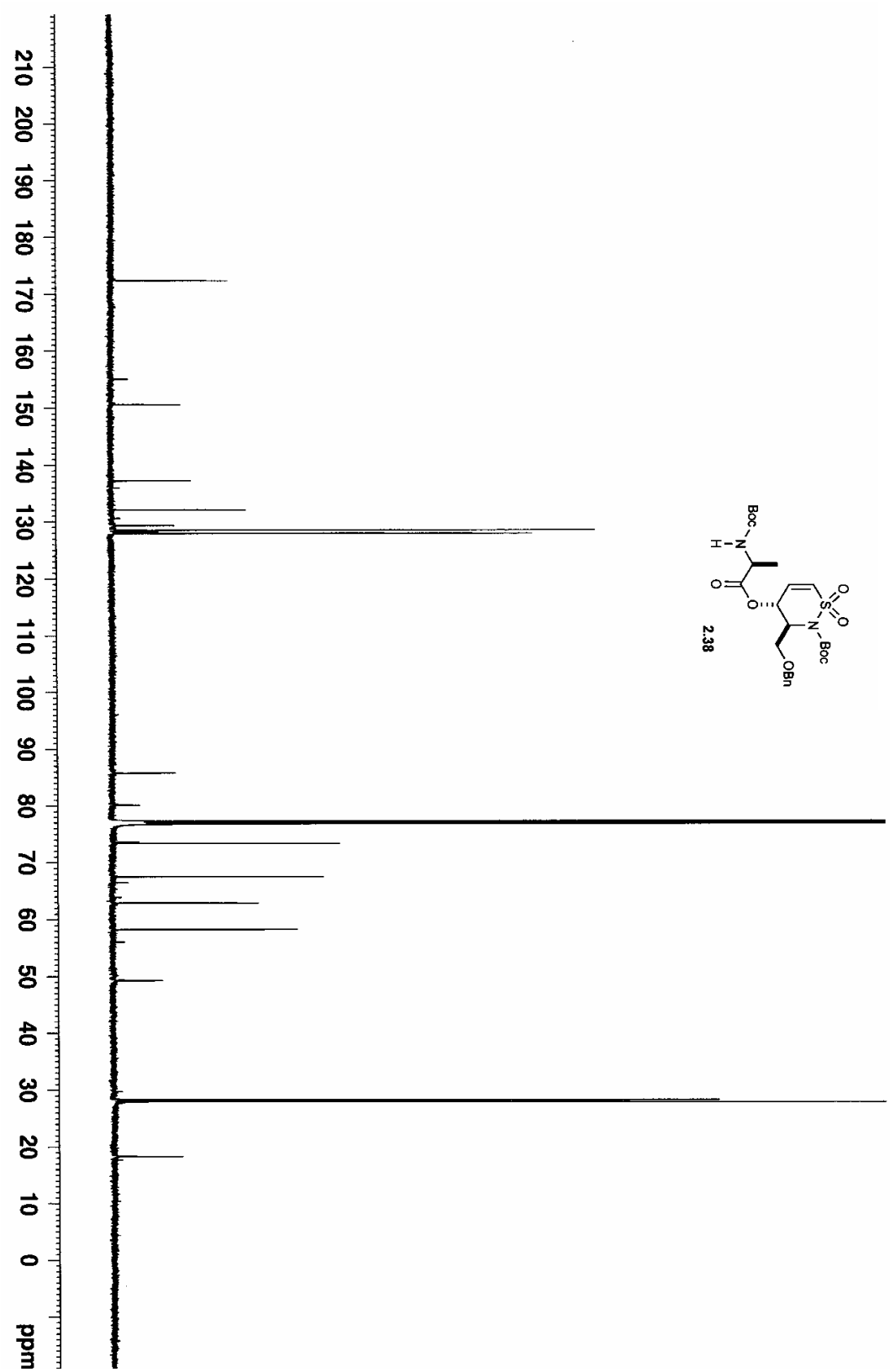
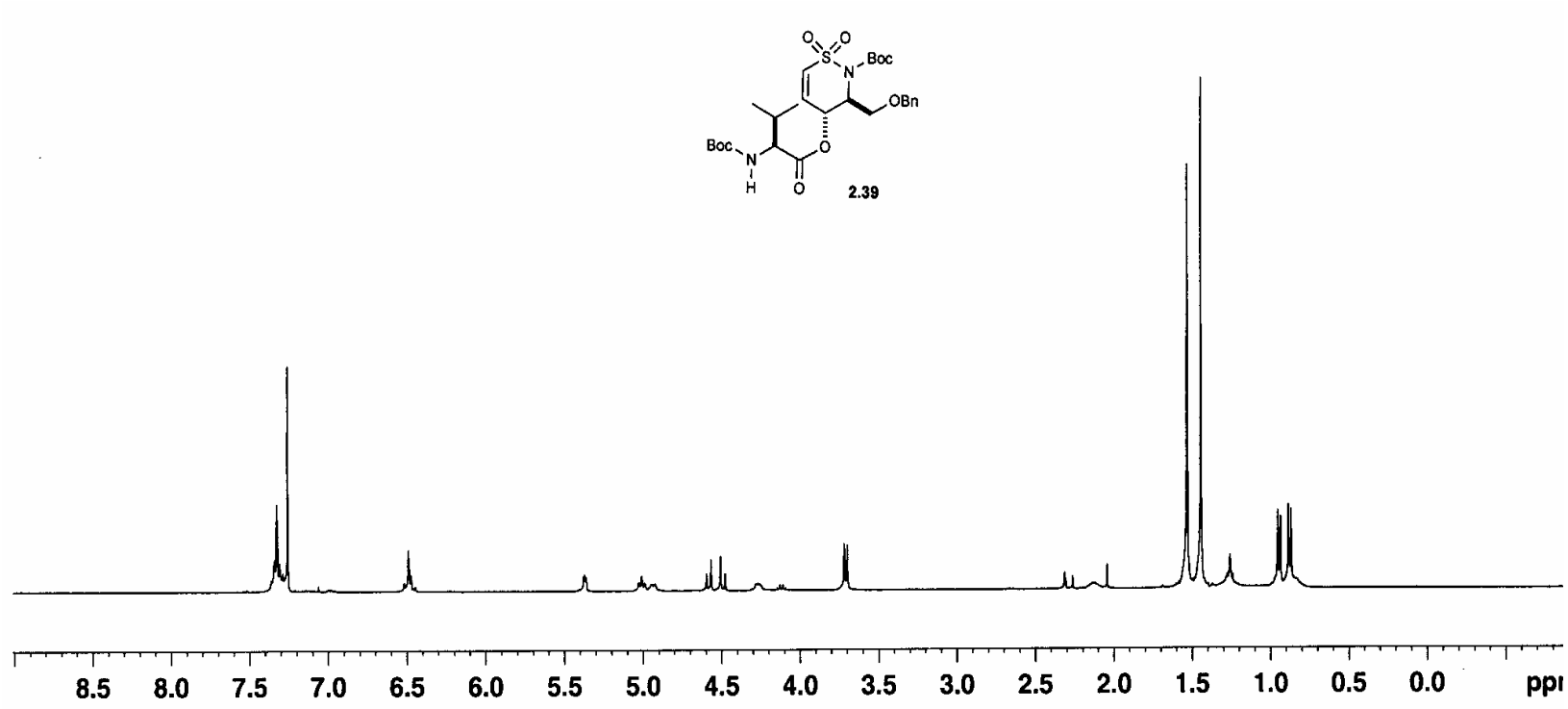
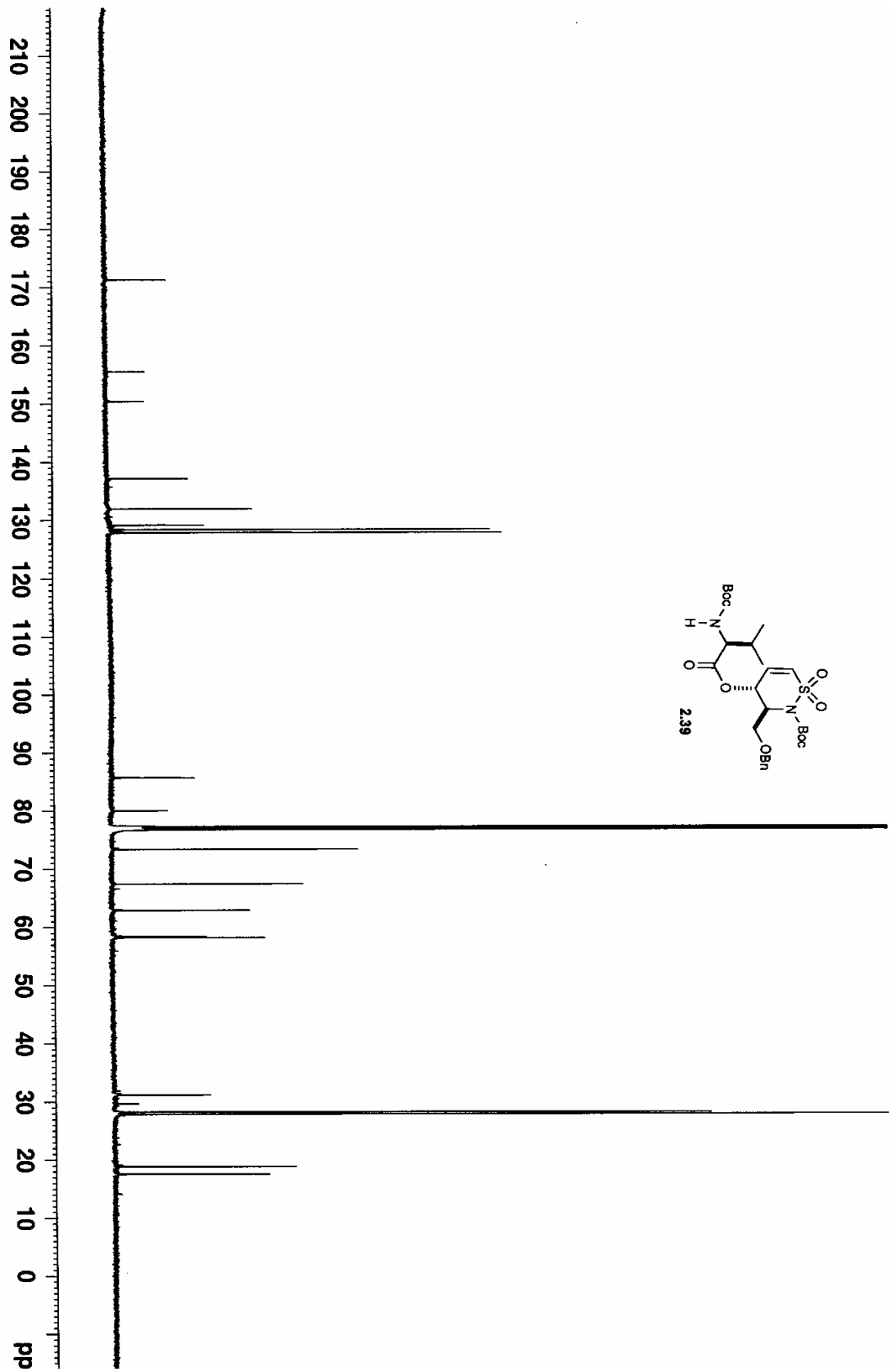
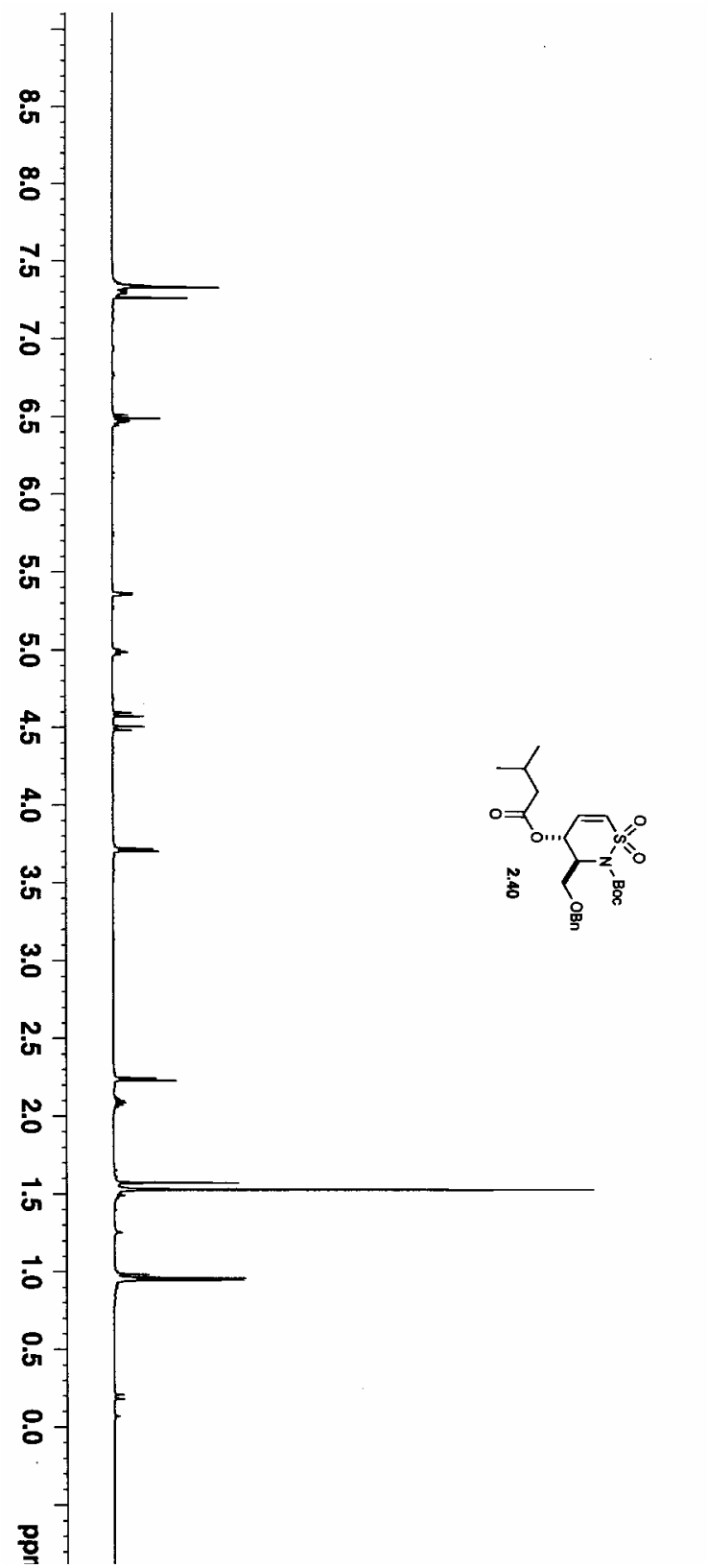
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
Boc
N
H
O
O
O
S
O
O
N
Boc
OBn
2.38


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
Boc
N
H
O
O
O
S
O
O
N
Boc
OBn
2.38


Boc
OBn
Boc
N
H
2.39
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppr


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 pp
Boc
N
H
O
O
O
S
O
O
N
Boc
OBn
2.39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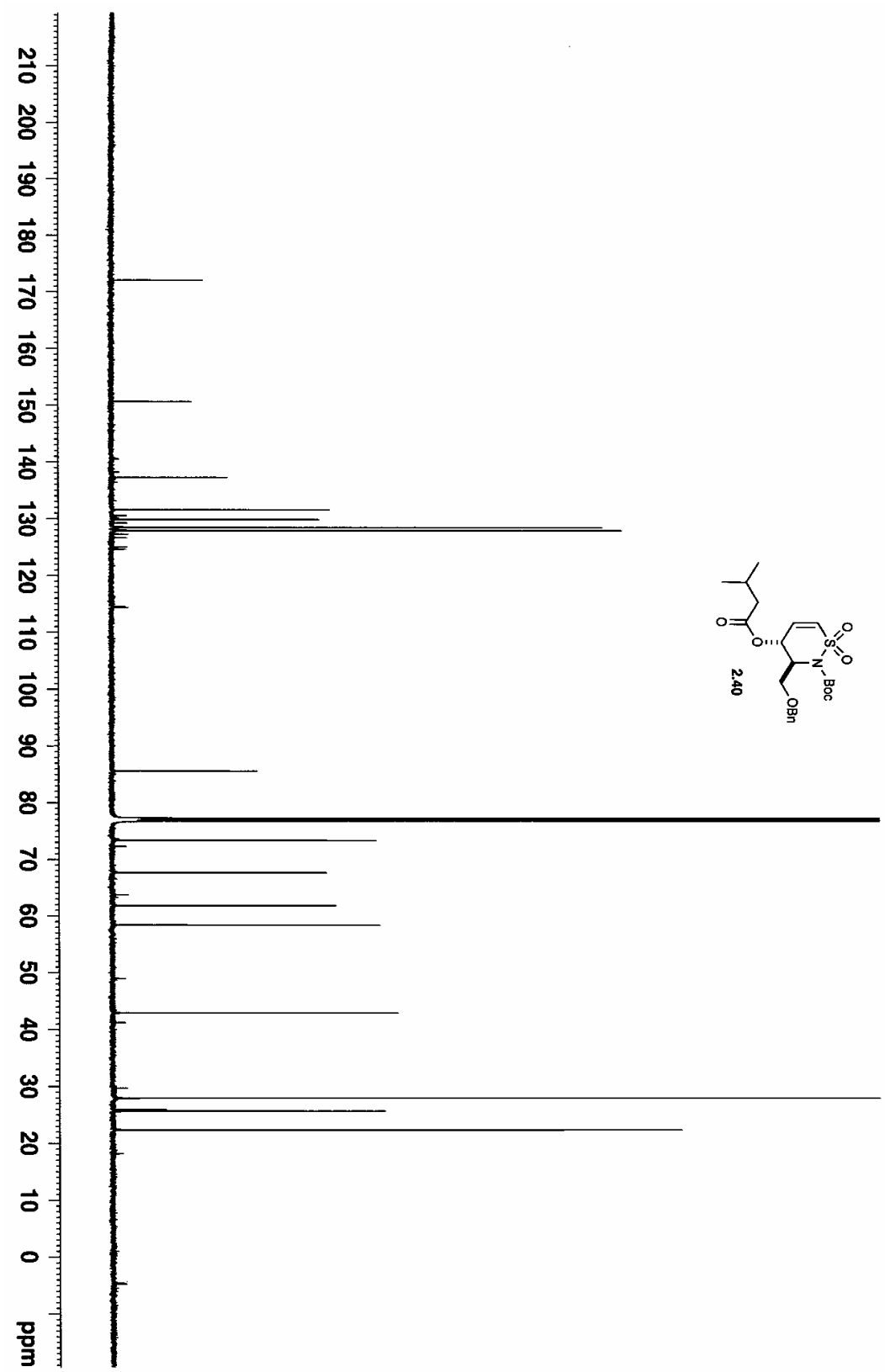
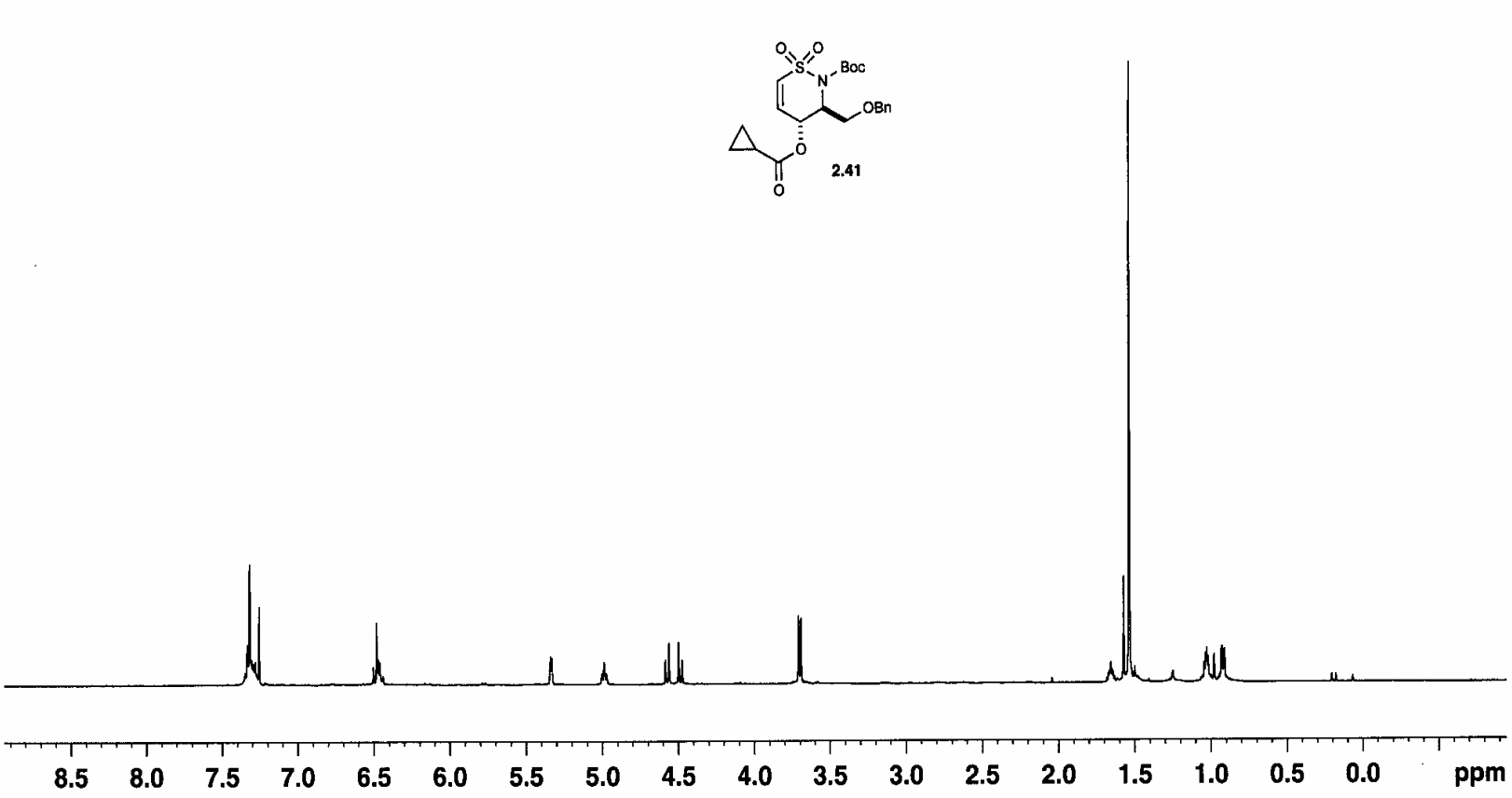
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
O
O
O
O
S
N
Boc
OBn
2.40


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
2.40
Boc
OBn


Boc
OBn
2.41
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7.0
6.5
6.0
5.5
5.0
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4.0
3.5
3.0
2.5
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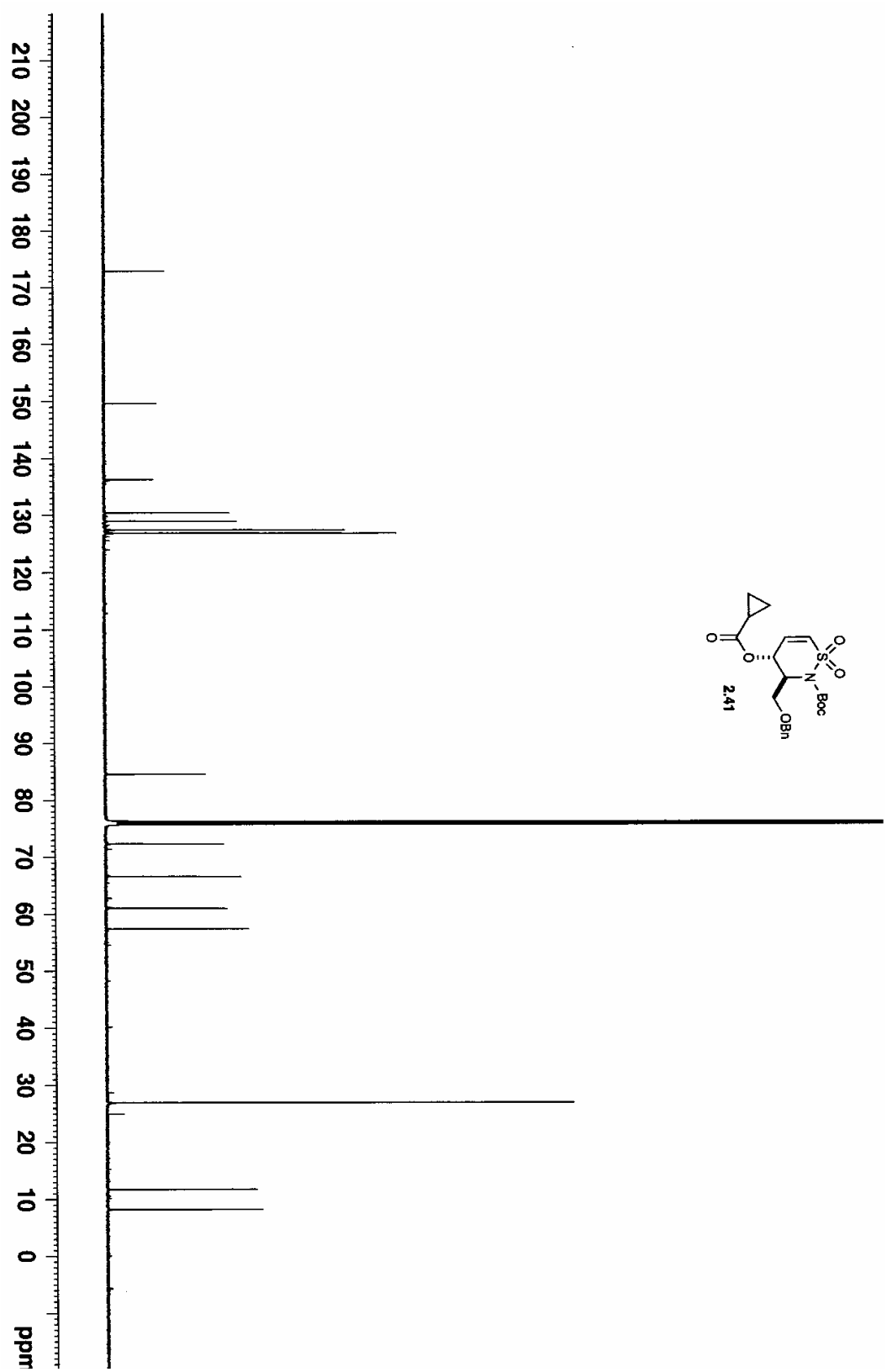
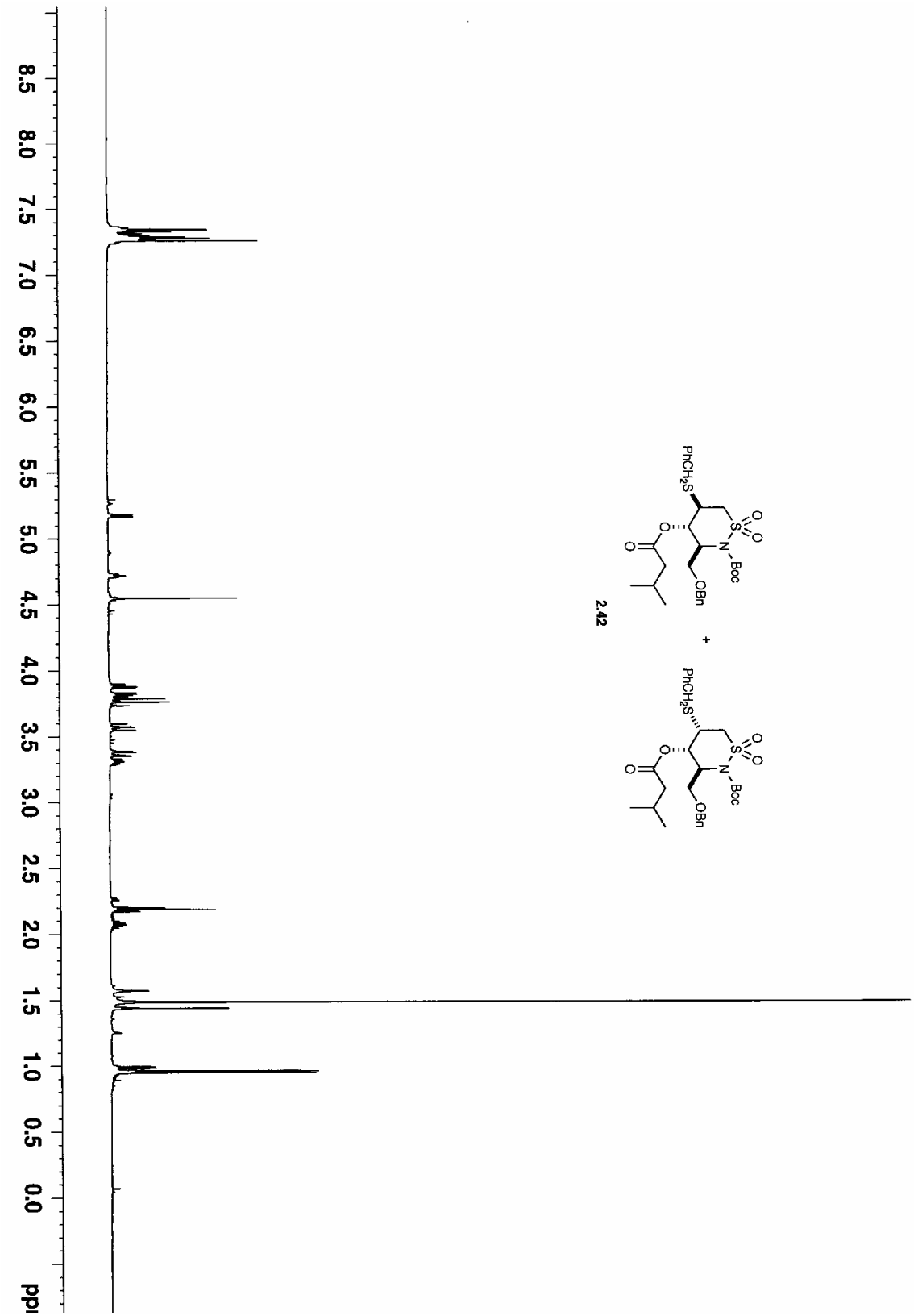
1.5
1.0
0.5
0.0
ppm


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm
O
O
O
O
S
N
Boc
OBn
2.41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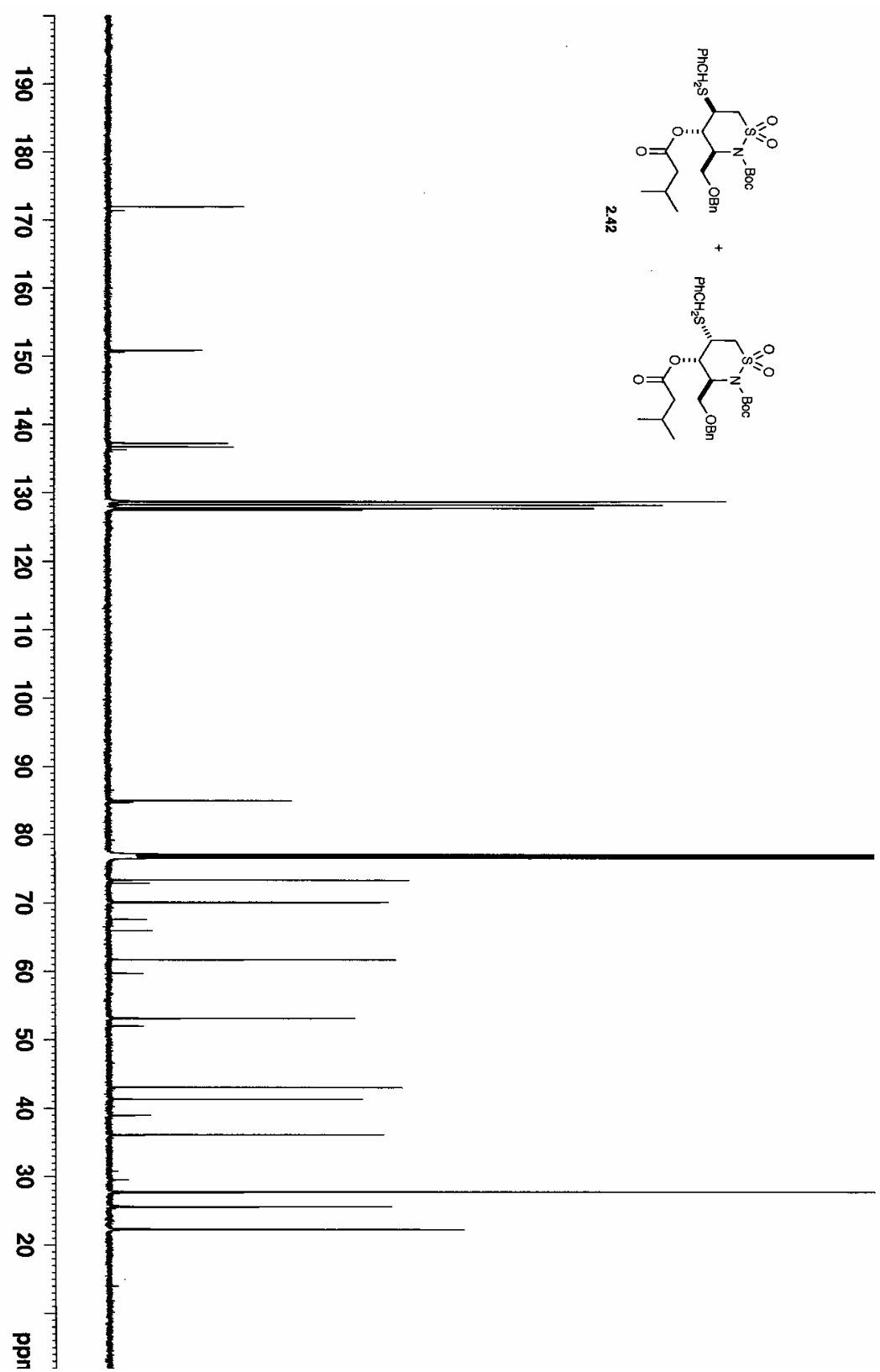
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
PhCH2S
O
O
S
N
Boc
OBn
O
O
+
PhCH2S
O
O
S
N
Boc
OBn
O
O

2.42


PhCH2S
O
O
S
N
Boc
OBn
O
O
2.42
+
PhCH2S
O
O
S
N
Boc
OBn
O
O
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180
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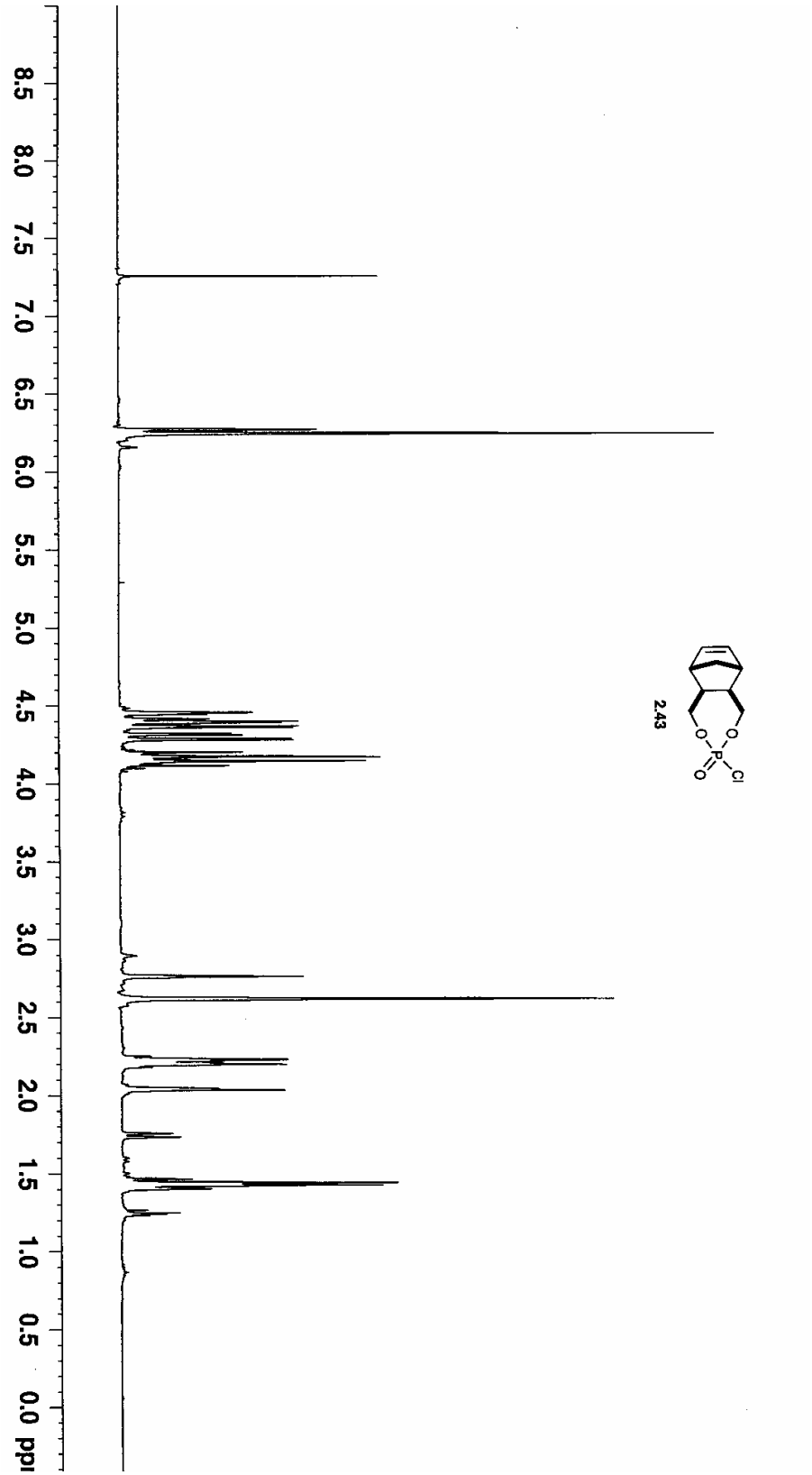
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


8.5
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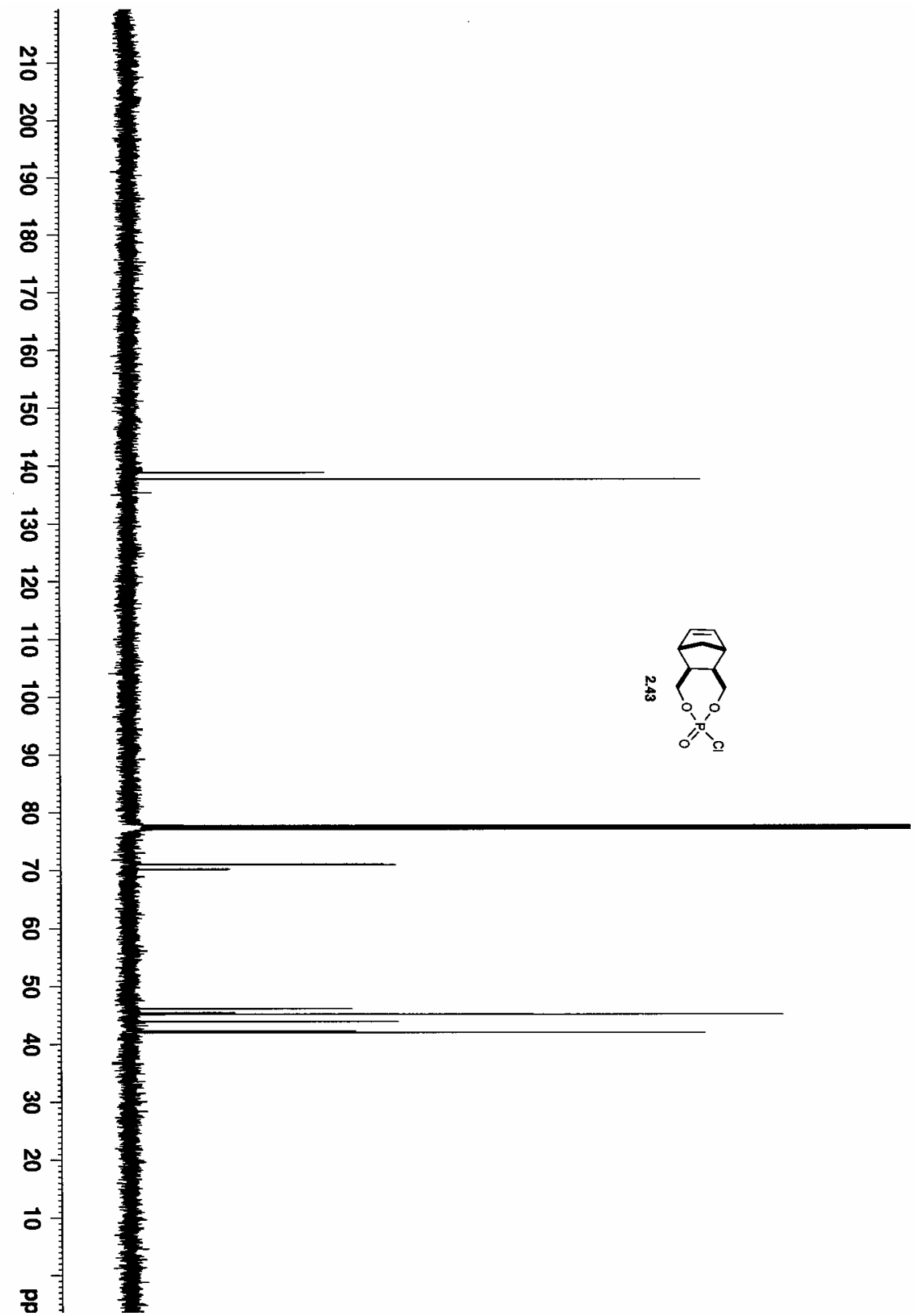
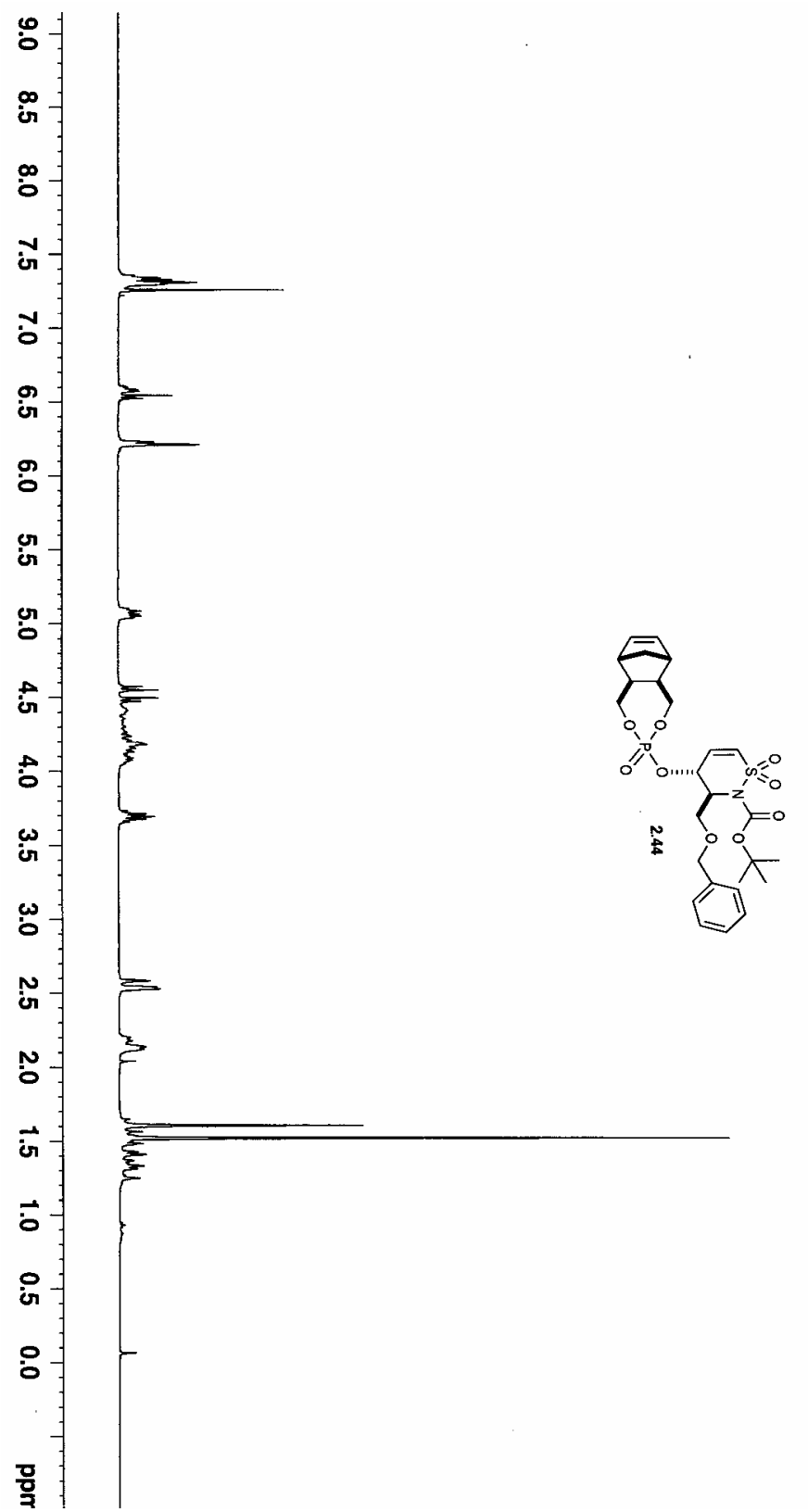
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0 ppm
2.43
O
O
P
Cl
O


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 pp
2.43
O
O
P
O
Cl


9.0
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8.0
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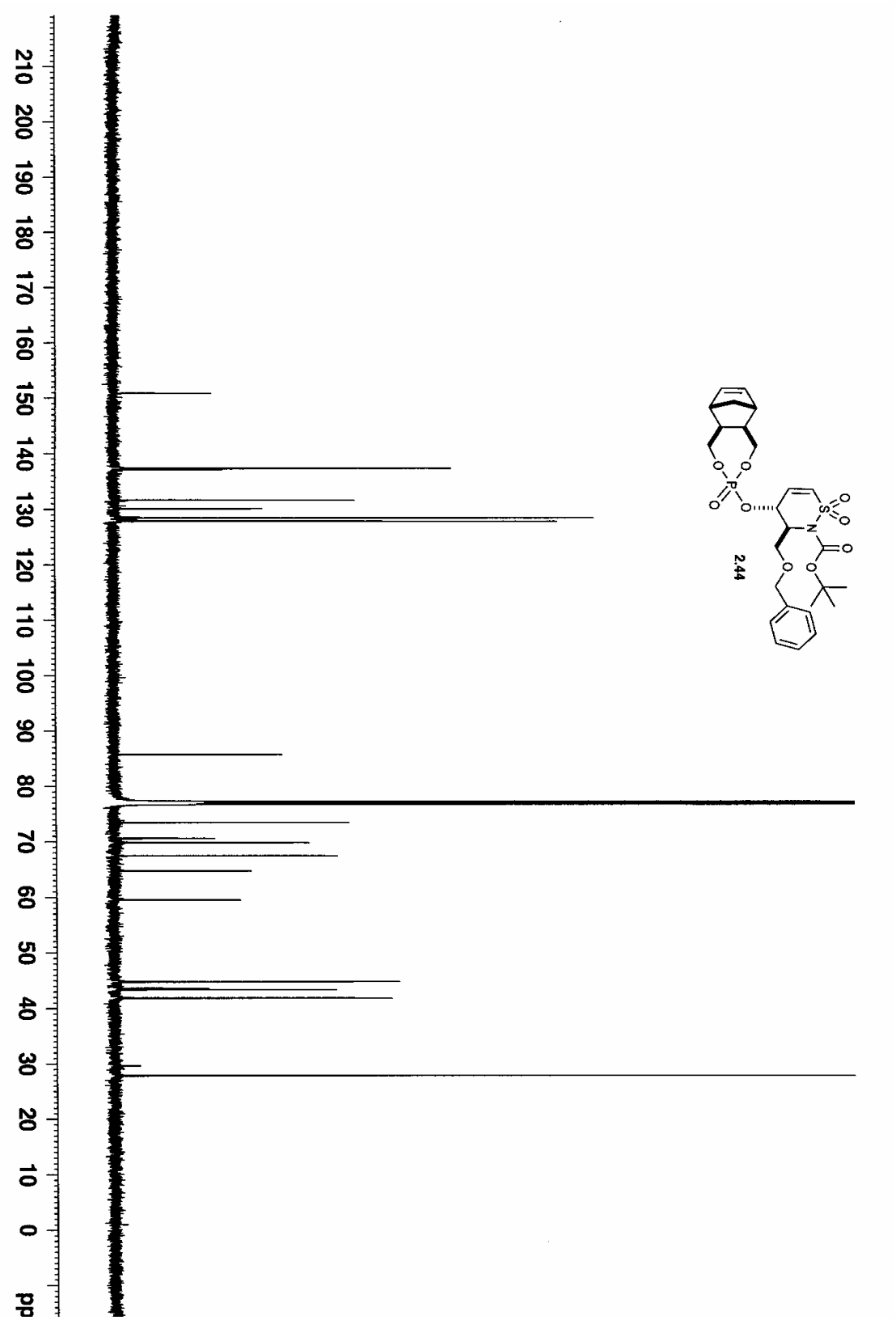
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
2.44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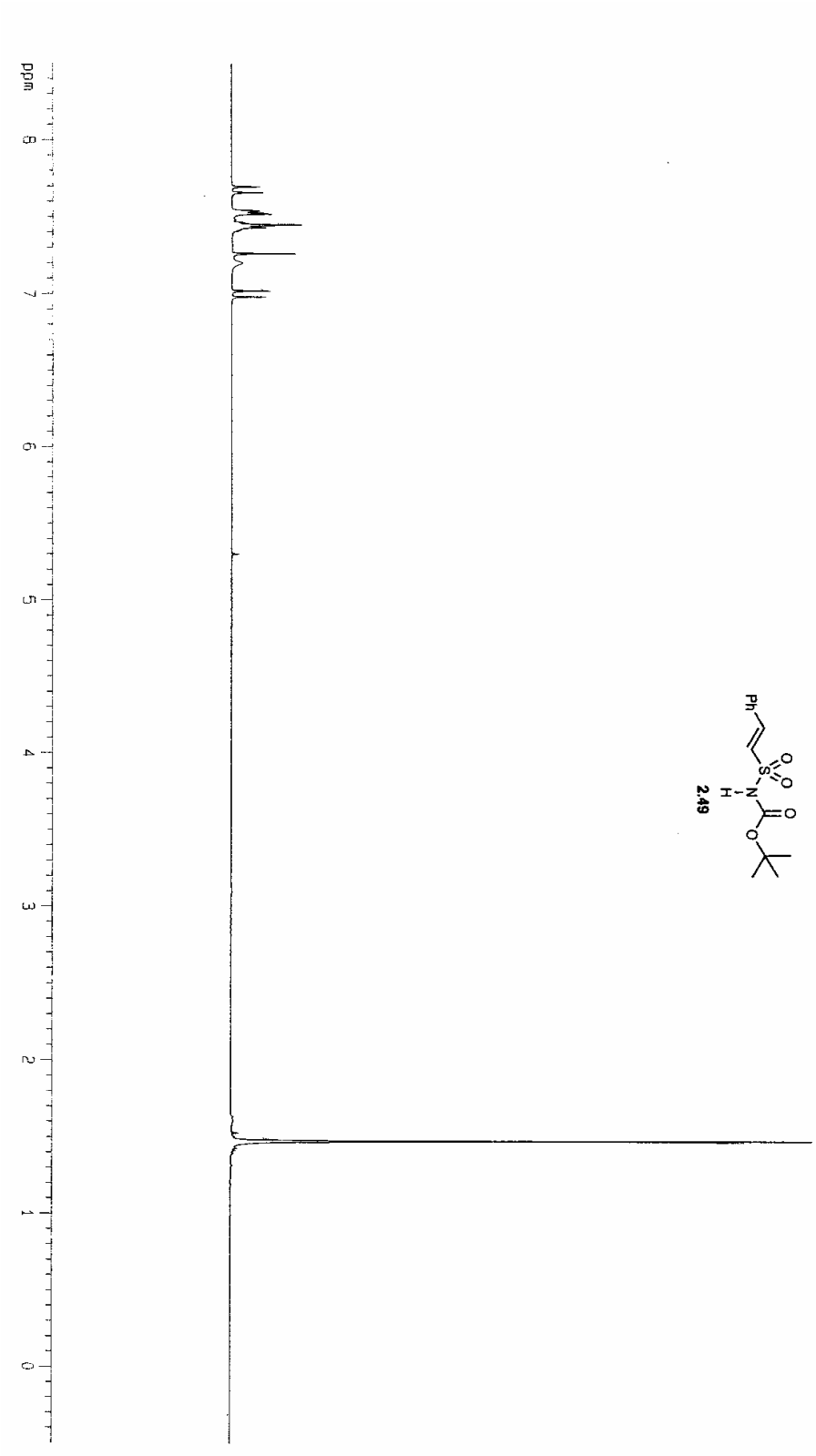
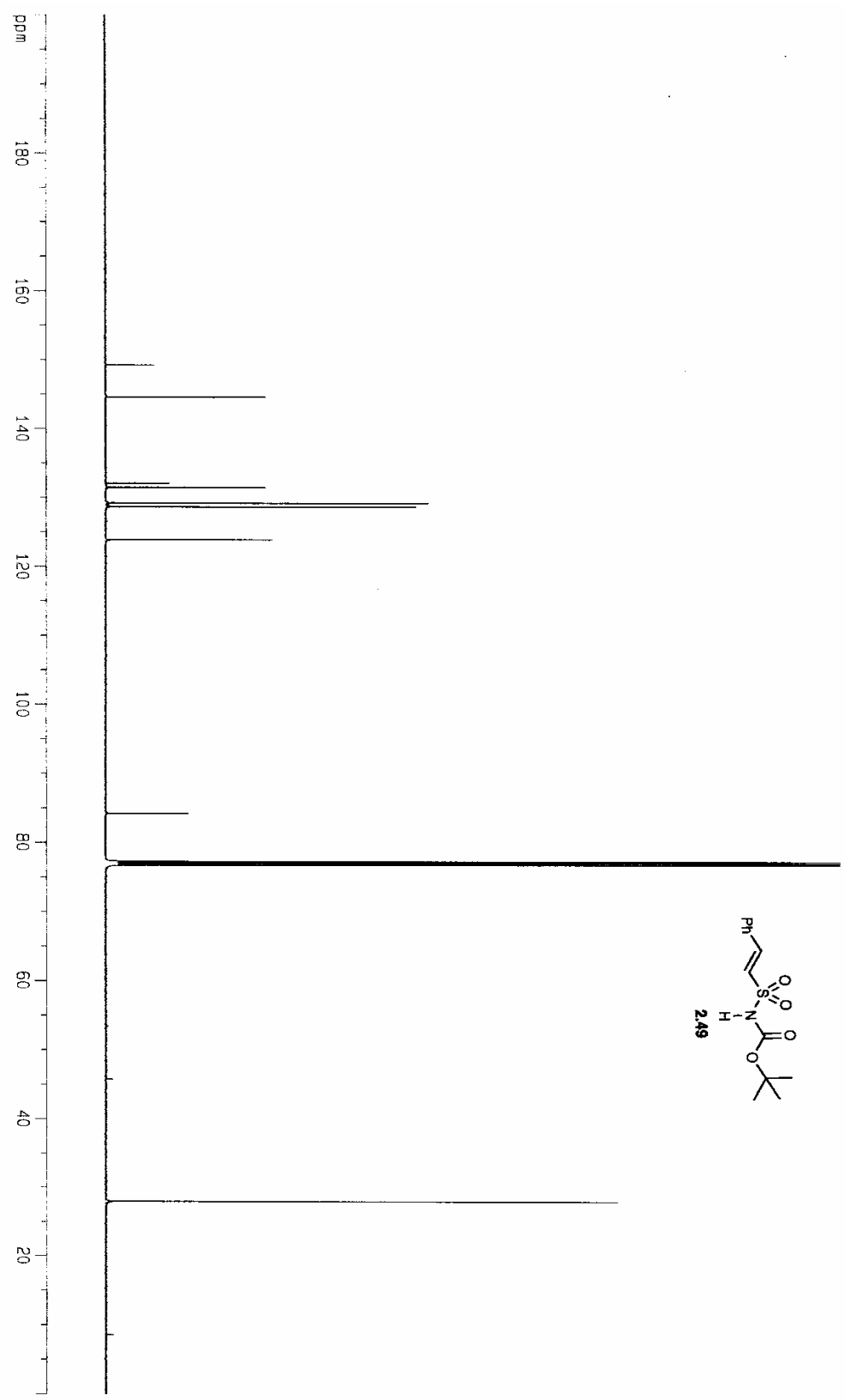
2.44


ppm
8
7
6
5
4
3
2
1
0
Ph
O
O
S
N
H
O
O
2.49


ppm
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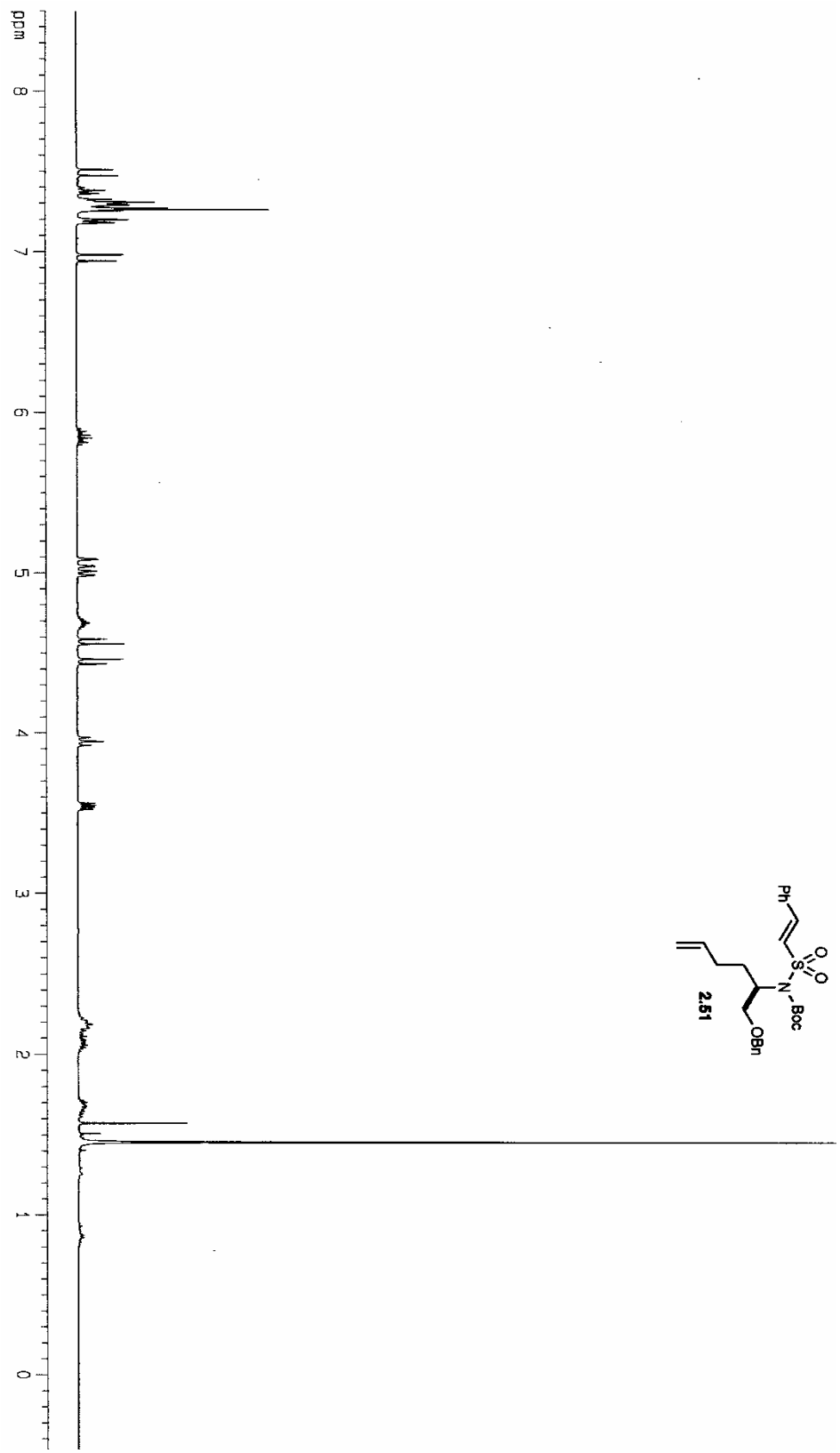
140
120
100
80
60
40
20
Ph
O
O
S
N
H
O
O
2.49


ppm
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O
S
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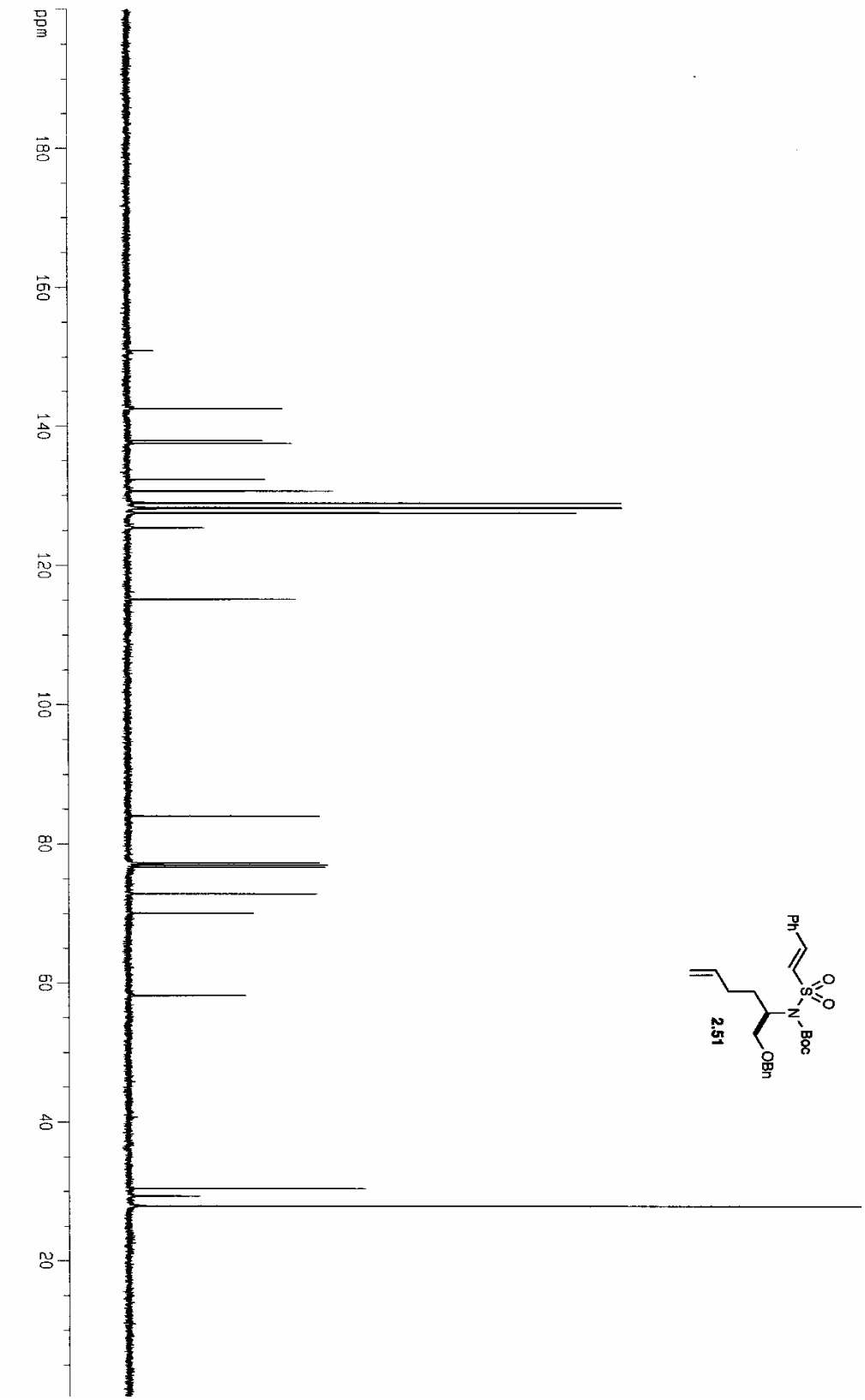
Boc
OBn
2.51


ppm
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100
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40
20
Ph
O
O
S
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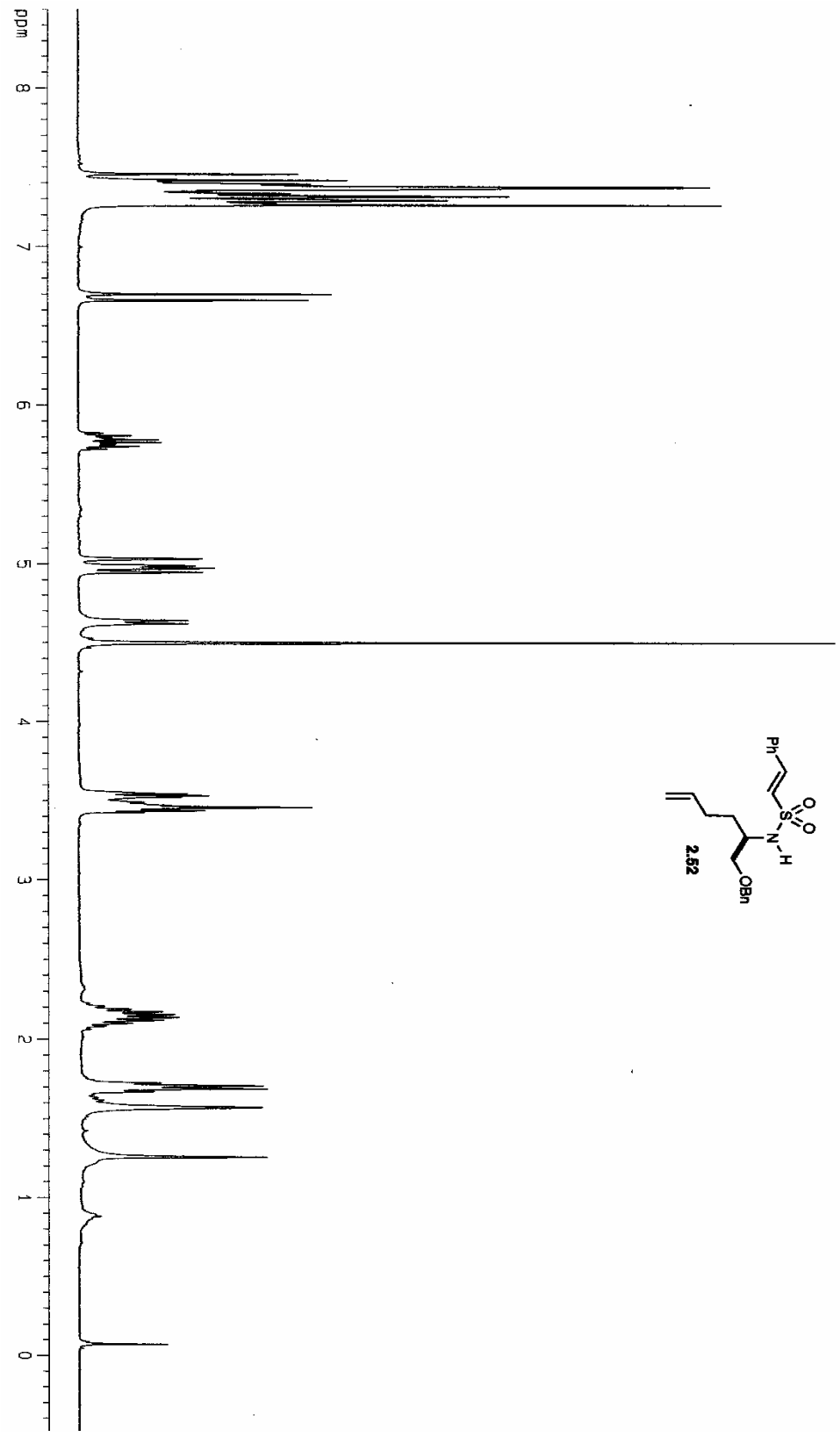
Boc
OBn
2.51


ppm
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2
1
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Ph
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S
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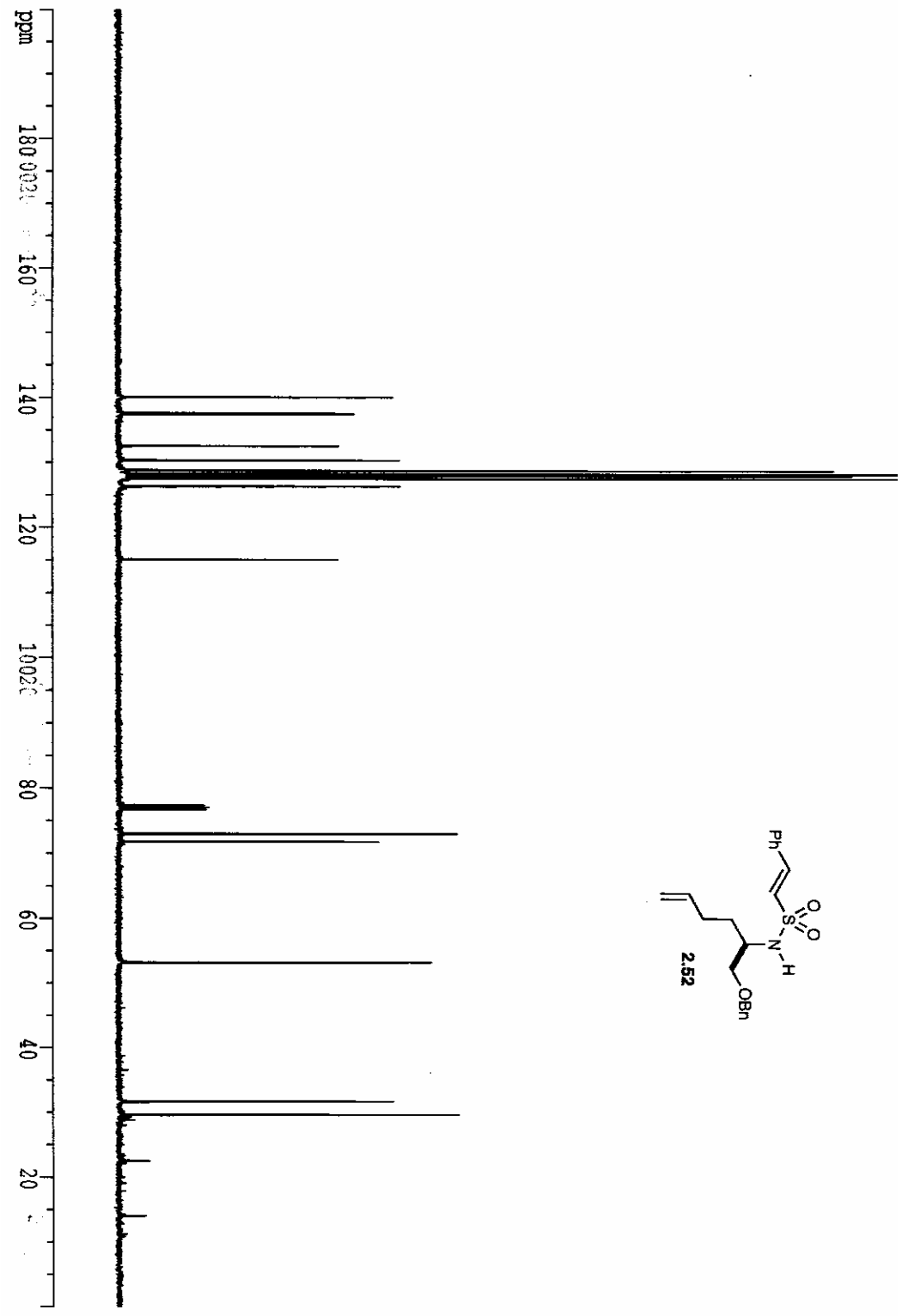
H
OBn
2.52


ppm
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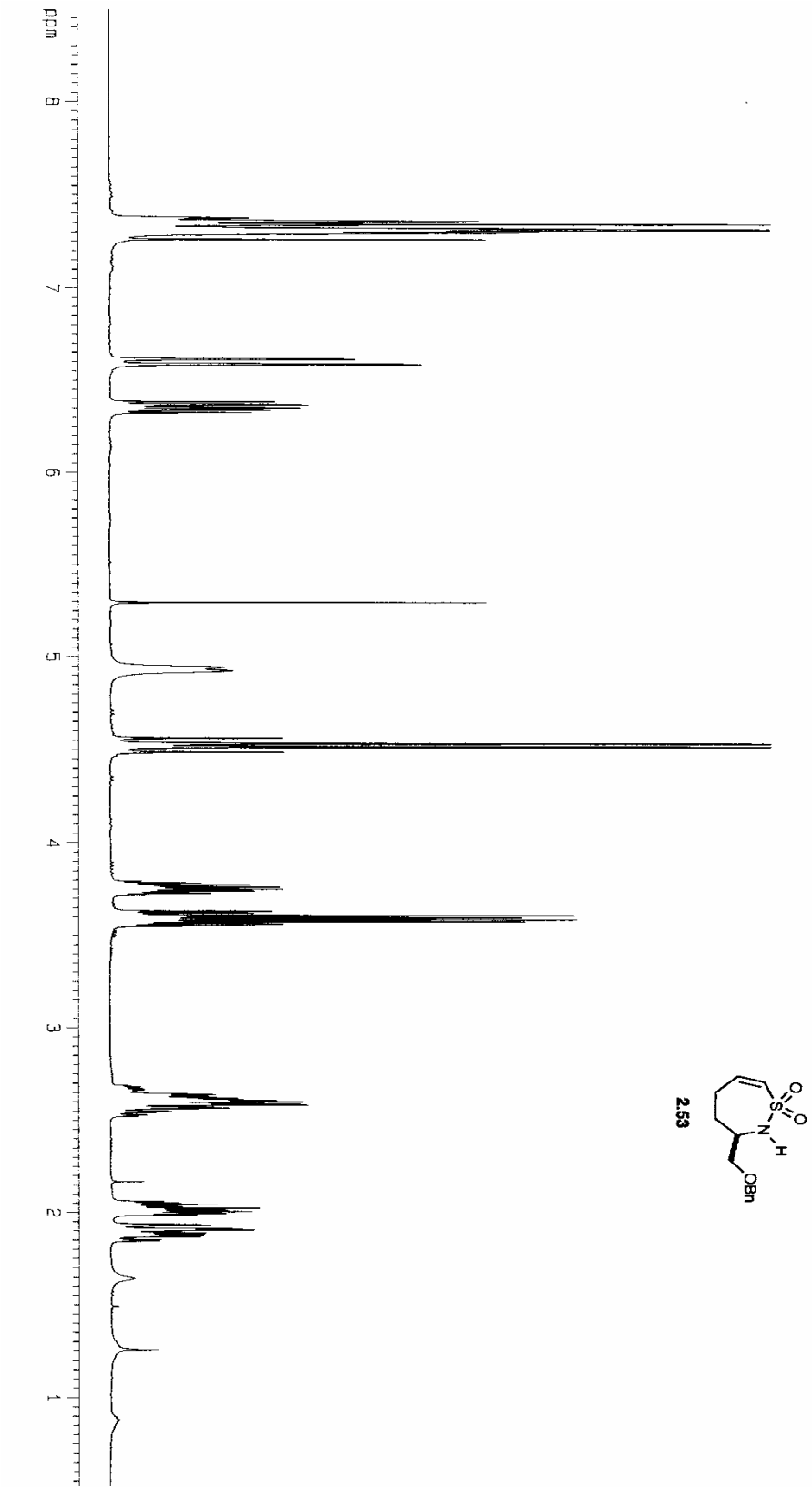
160
140
120
80
60
40
20
Ph
O
O
S
N
H
OBn
2.52


ppm
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4
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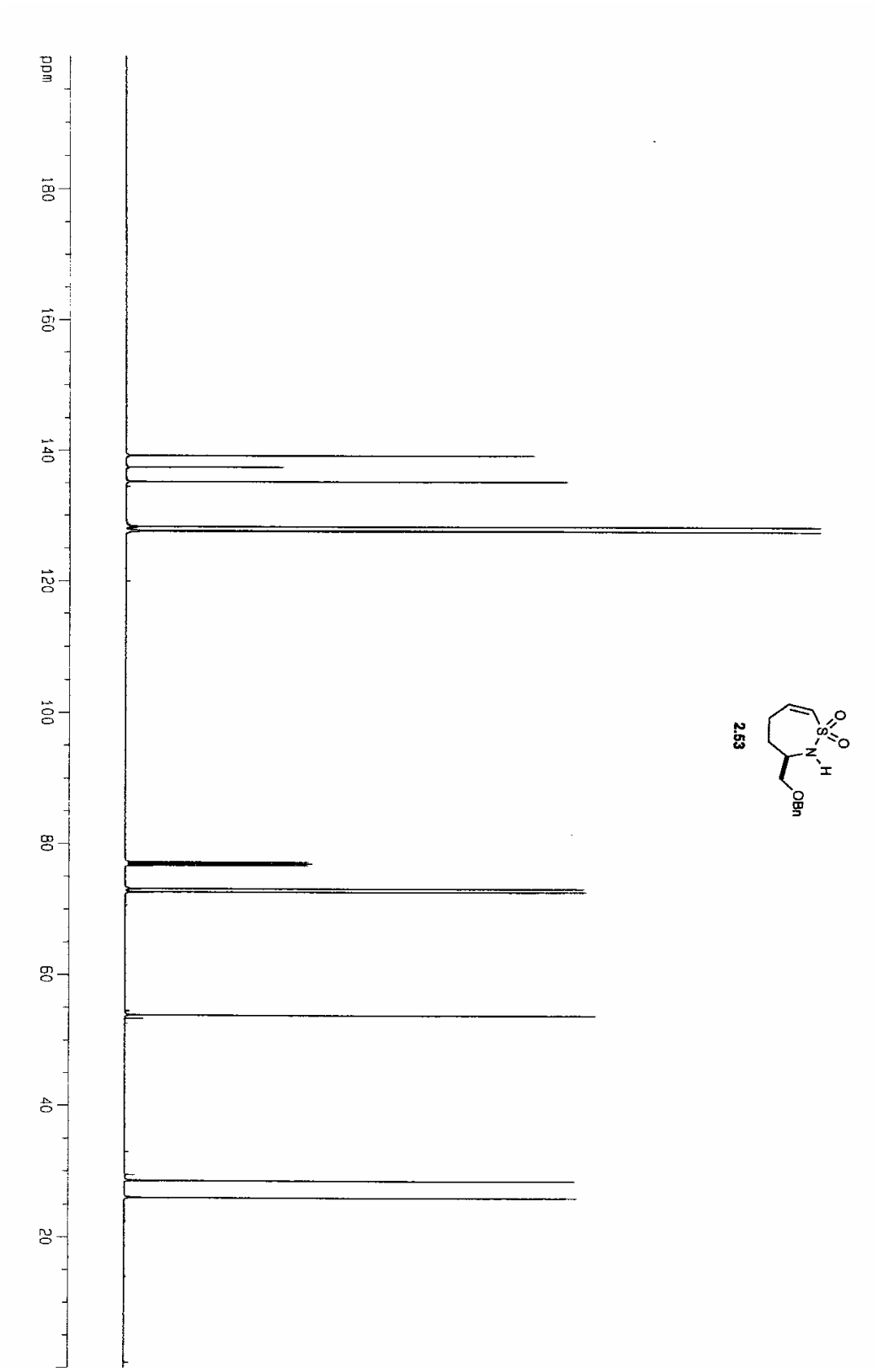
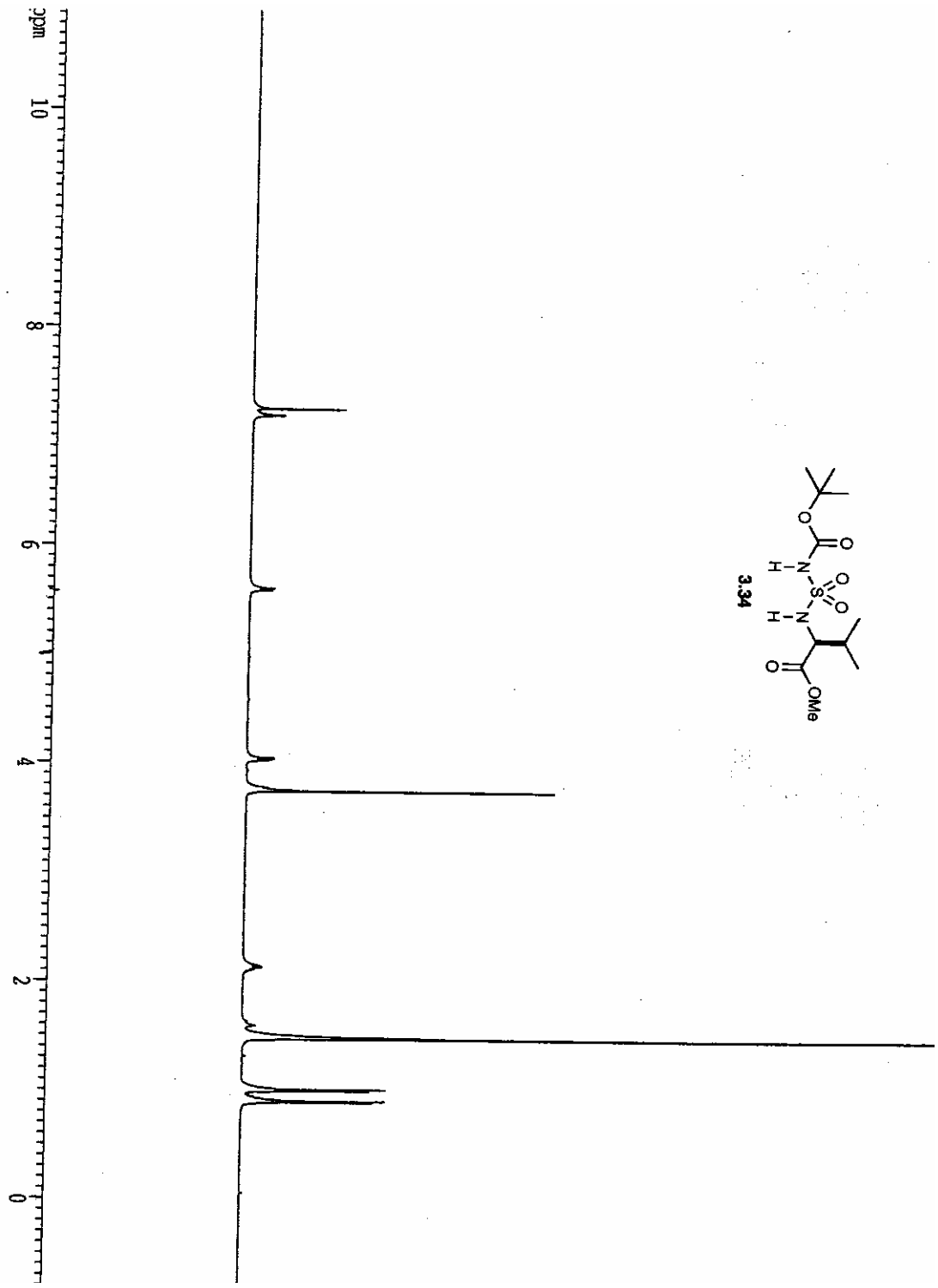
O
N
H
OBn
2.53


ppm
180
160
140
120
100
80
60
40
20
2.53
OBn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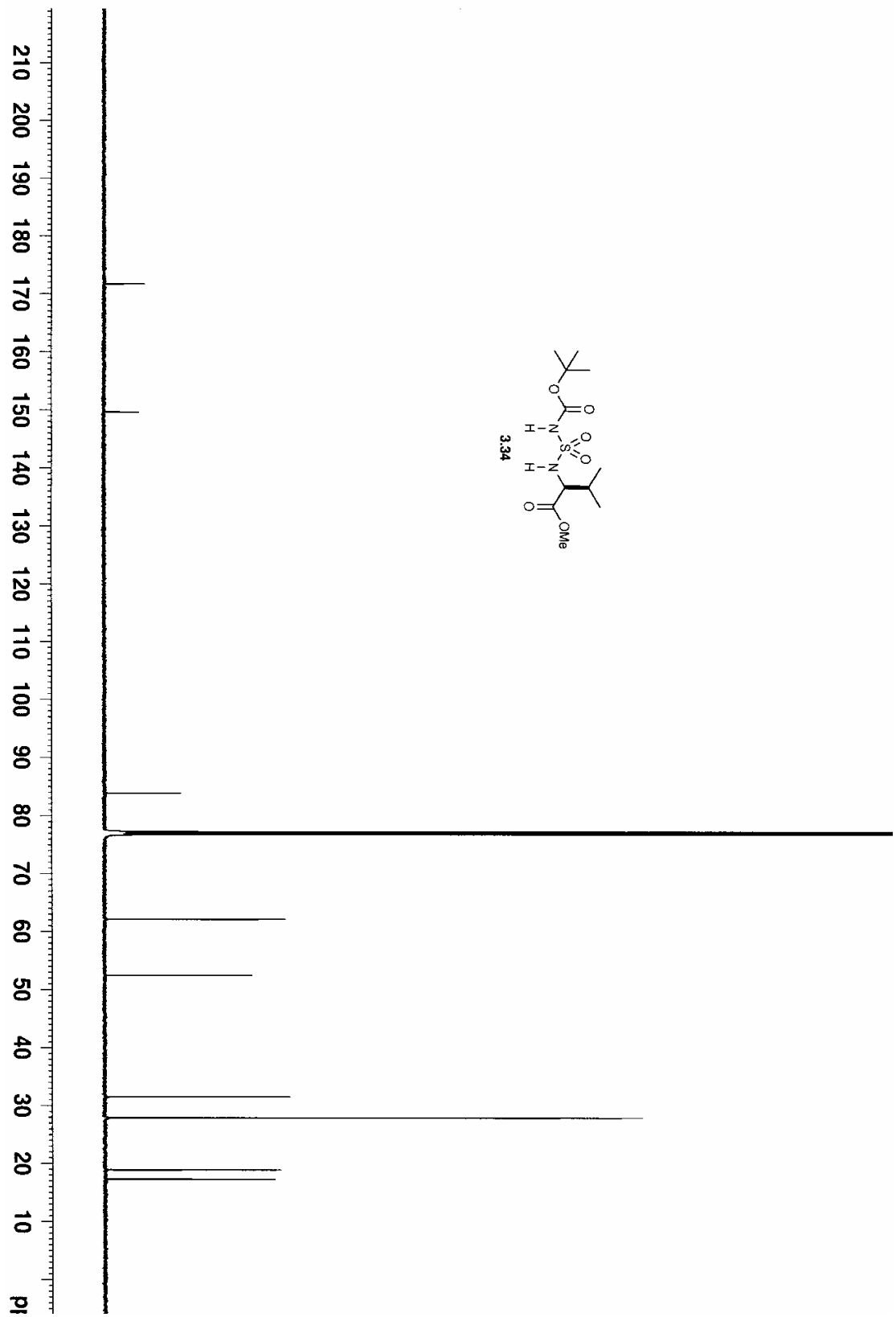
OMe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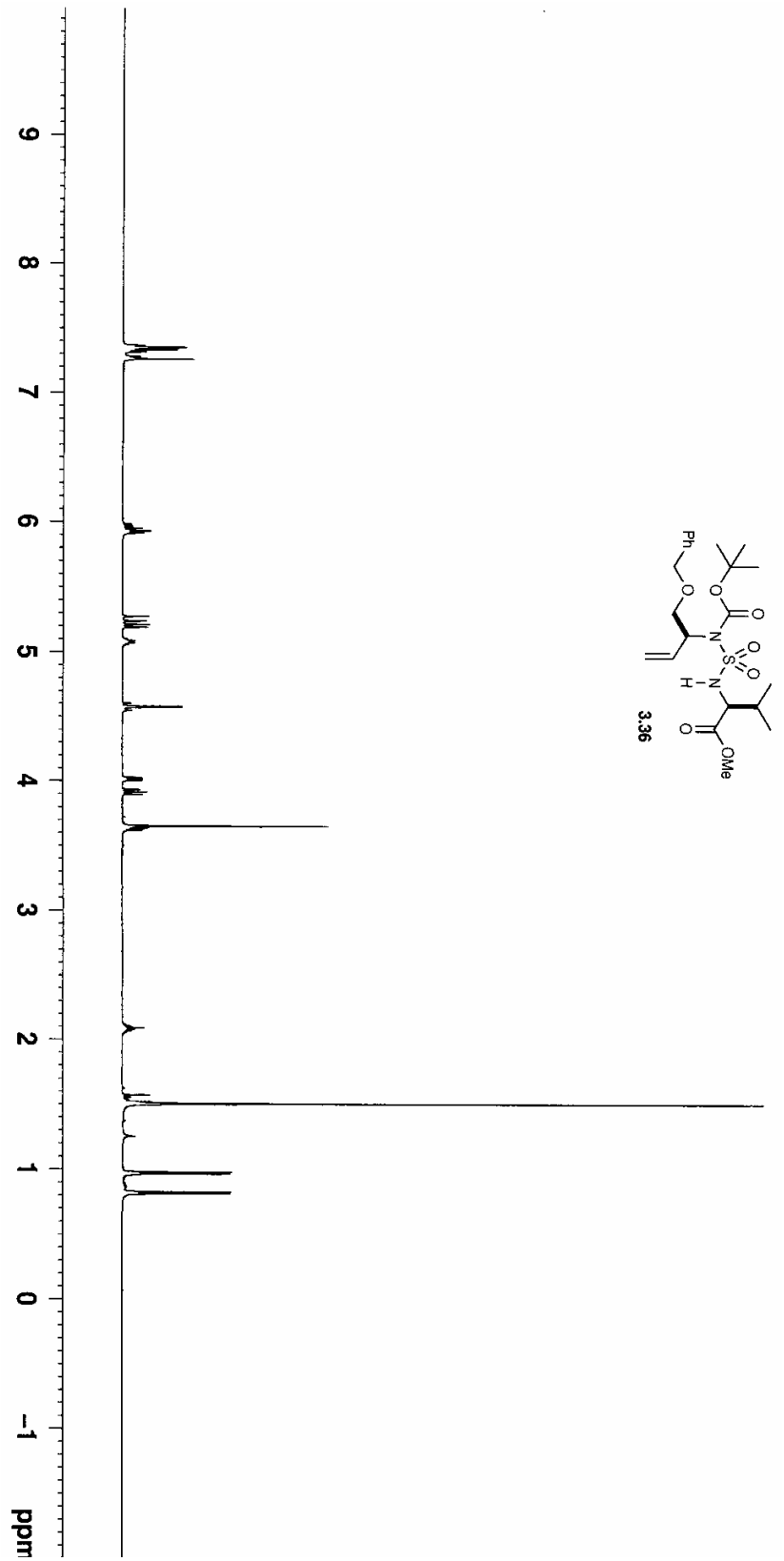
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ppm
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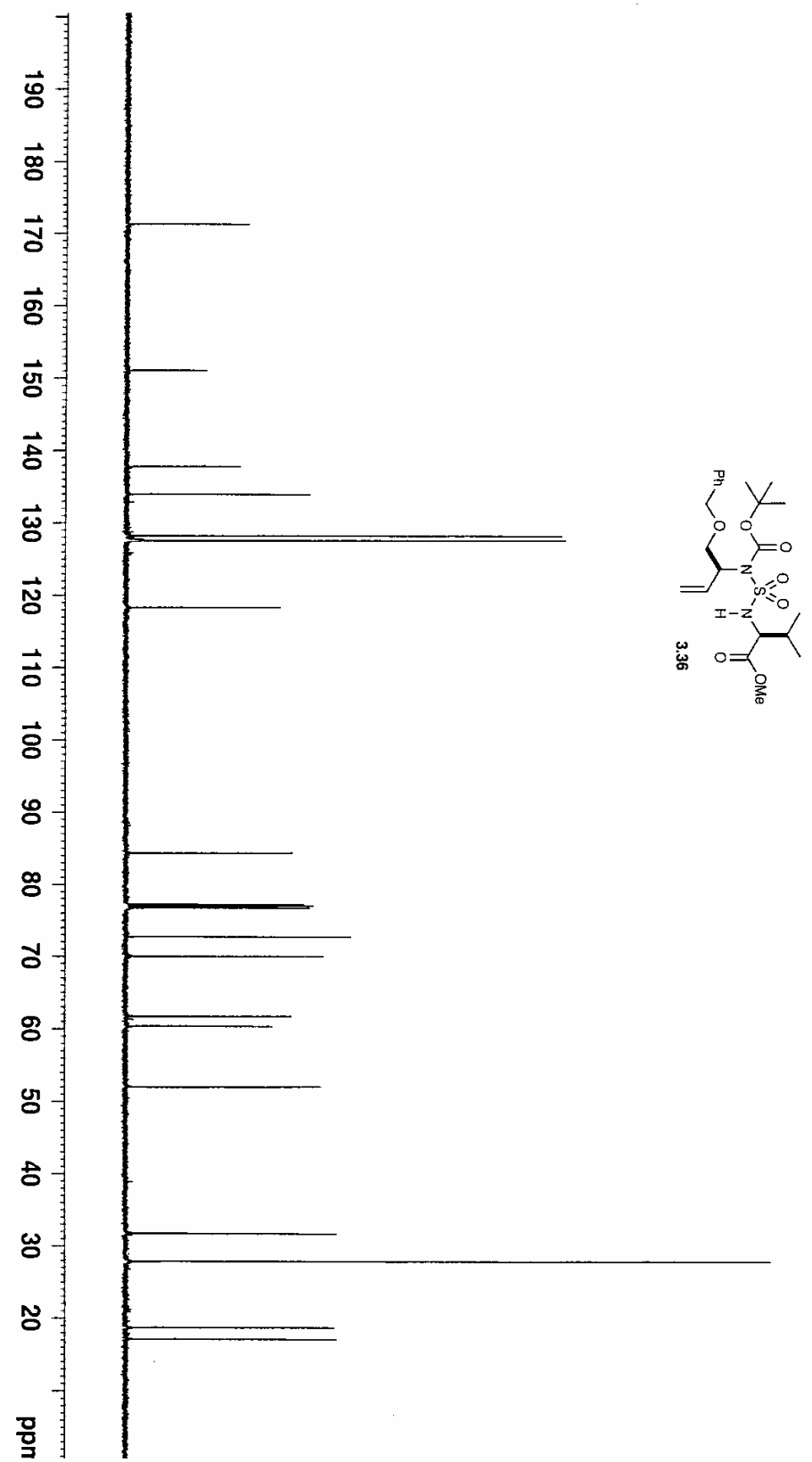
N
H
O
OMe
3.36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ppm
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O
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O
O
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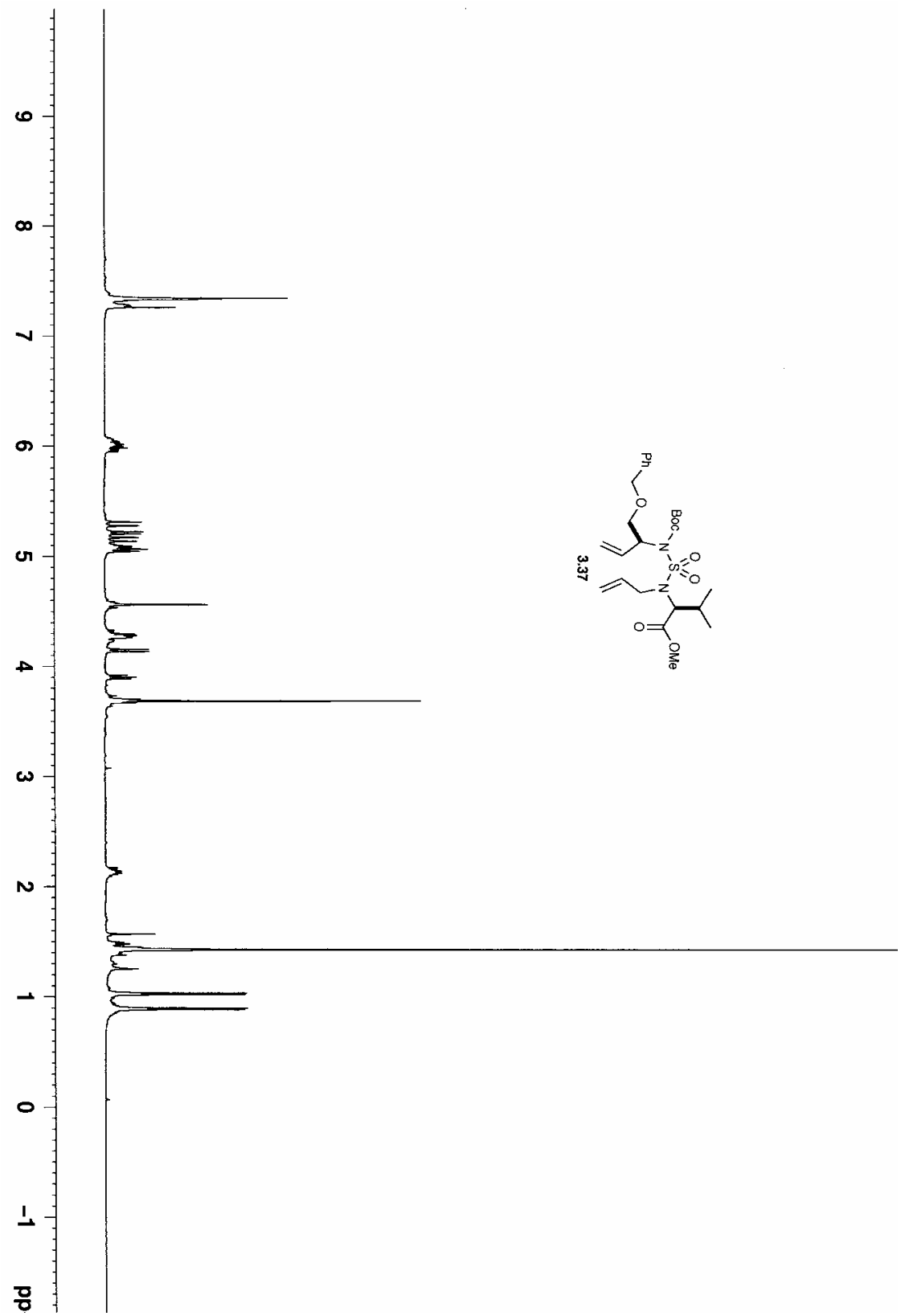
O
OMe
3.36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-1
pp
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Boc
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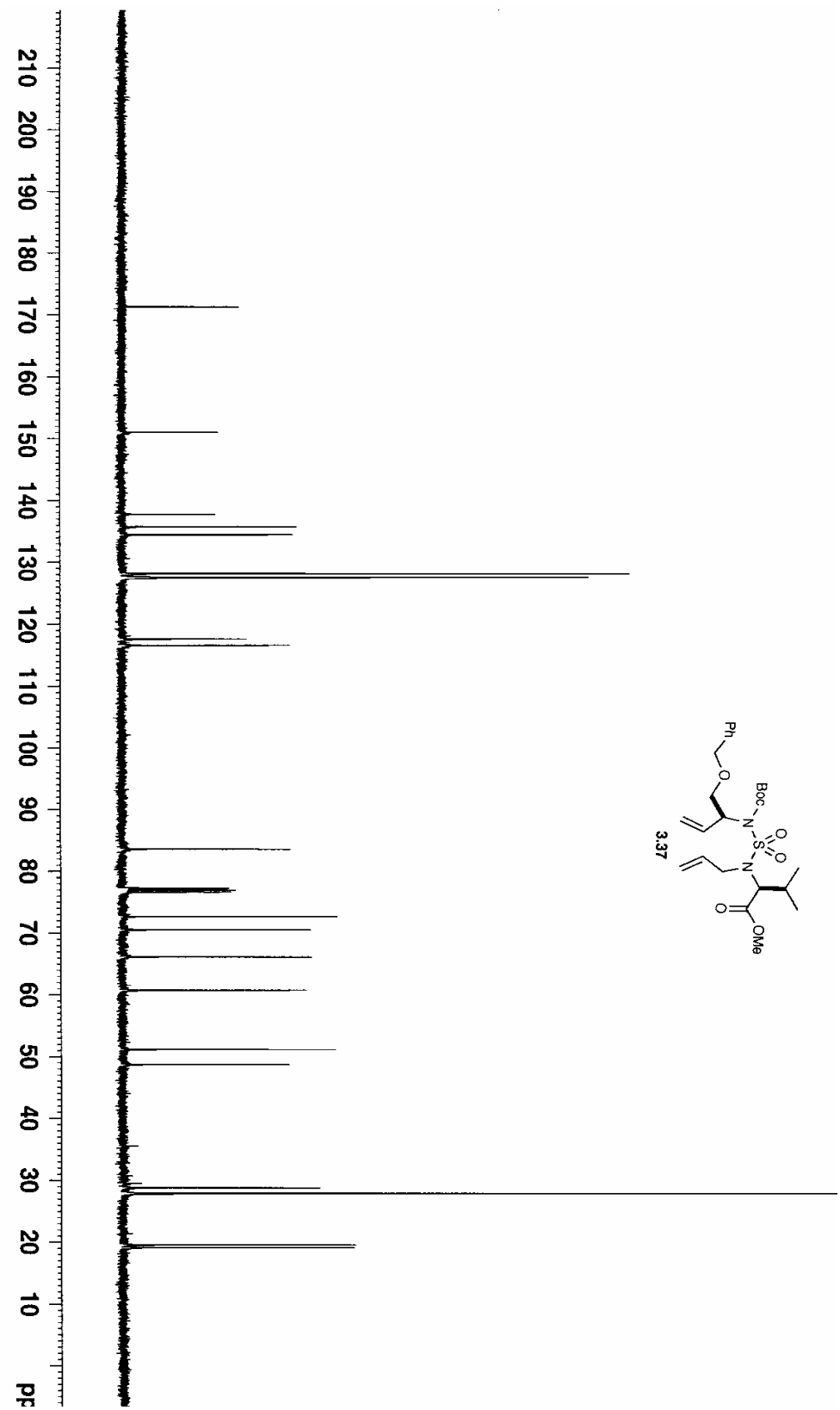
O
OMe
3.37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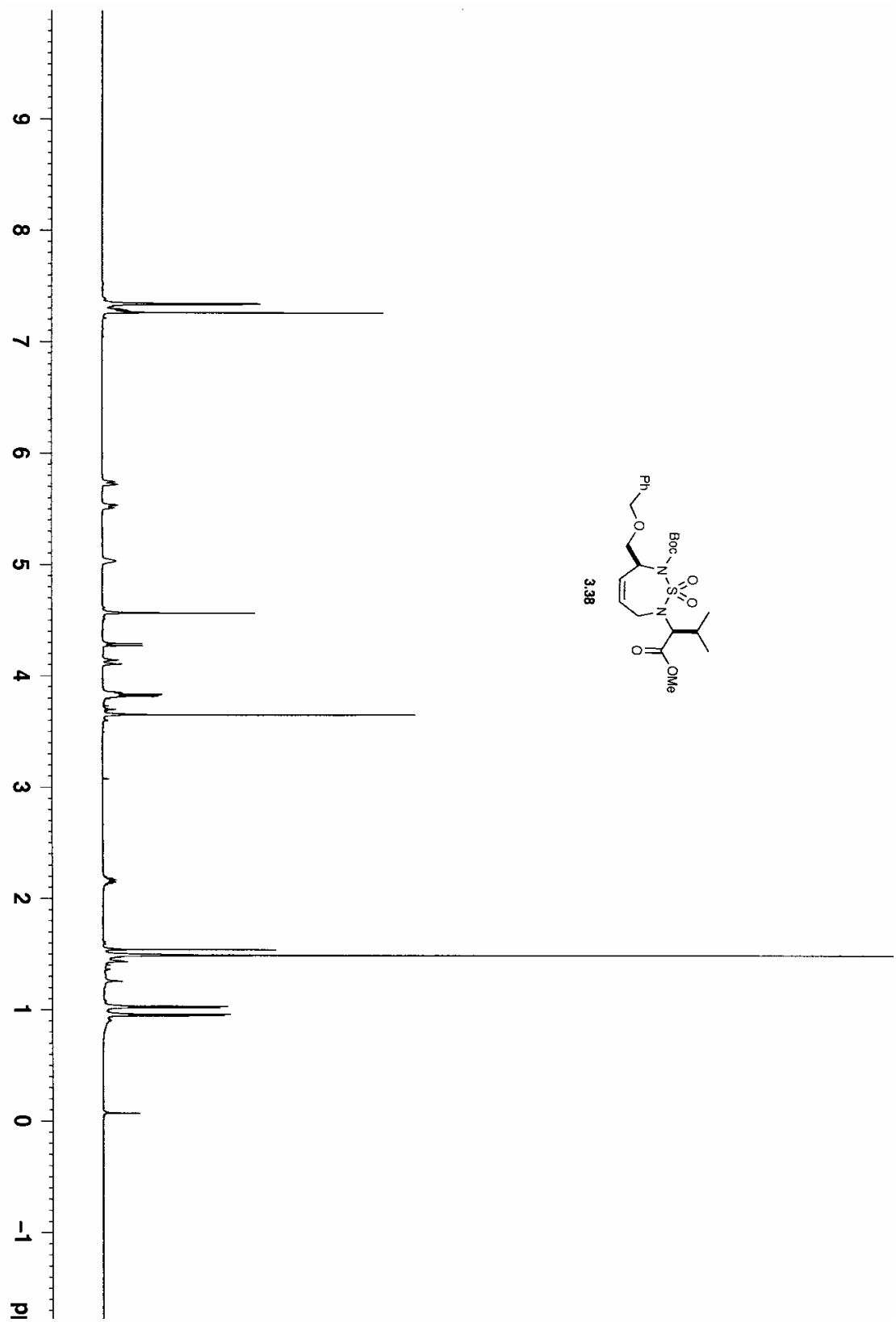
O
OMe
3.37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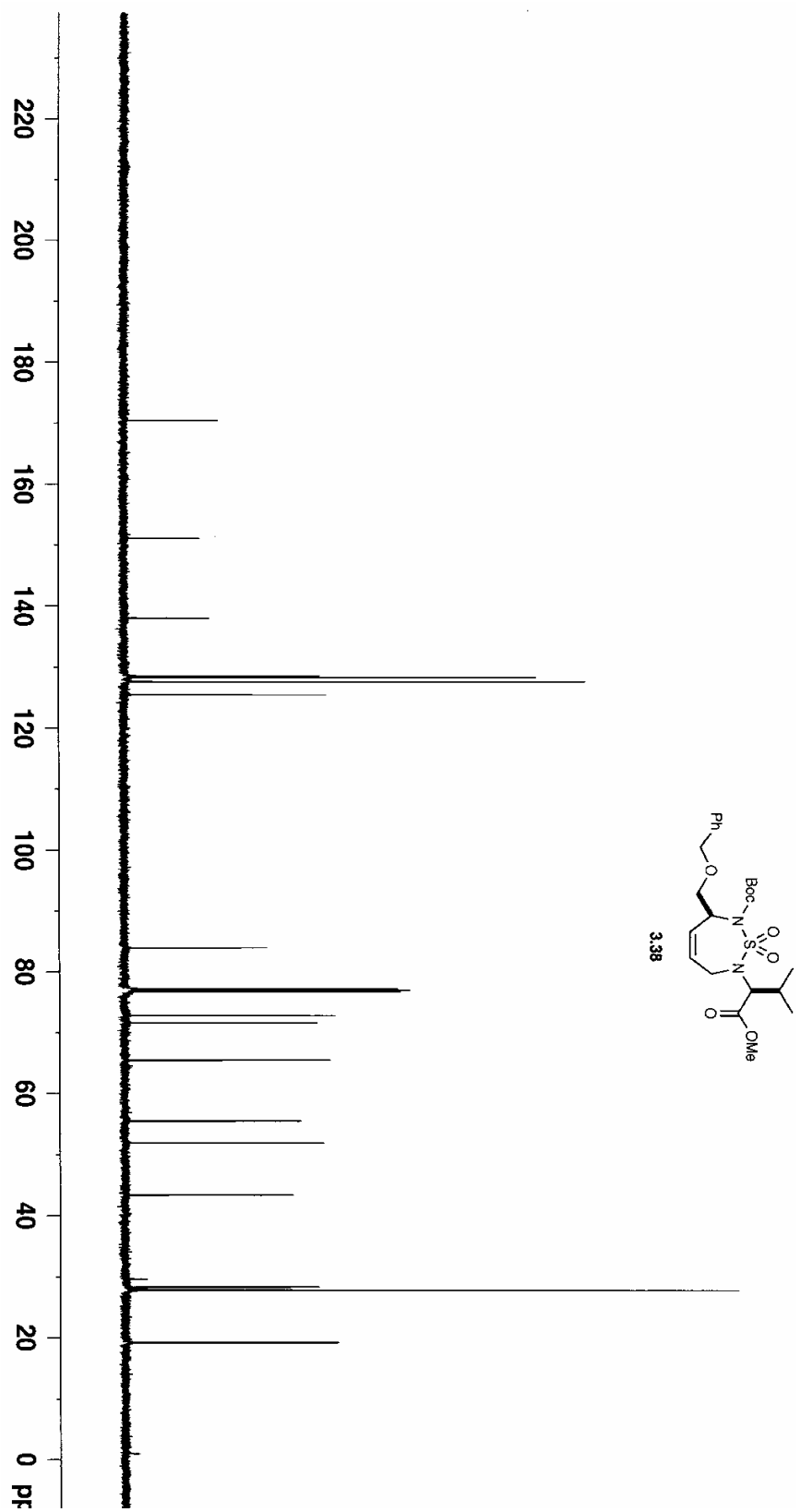
O
OMe
3.38

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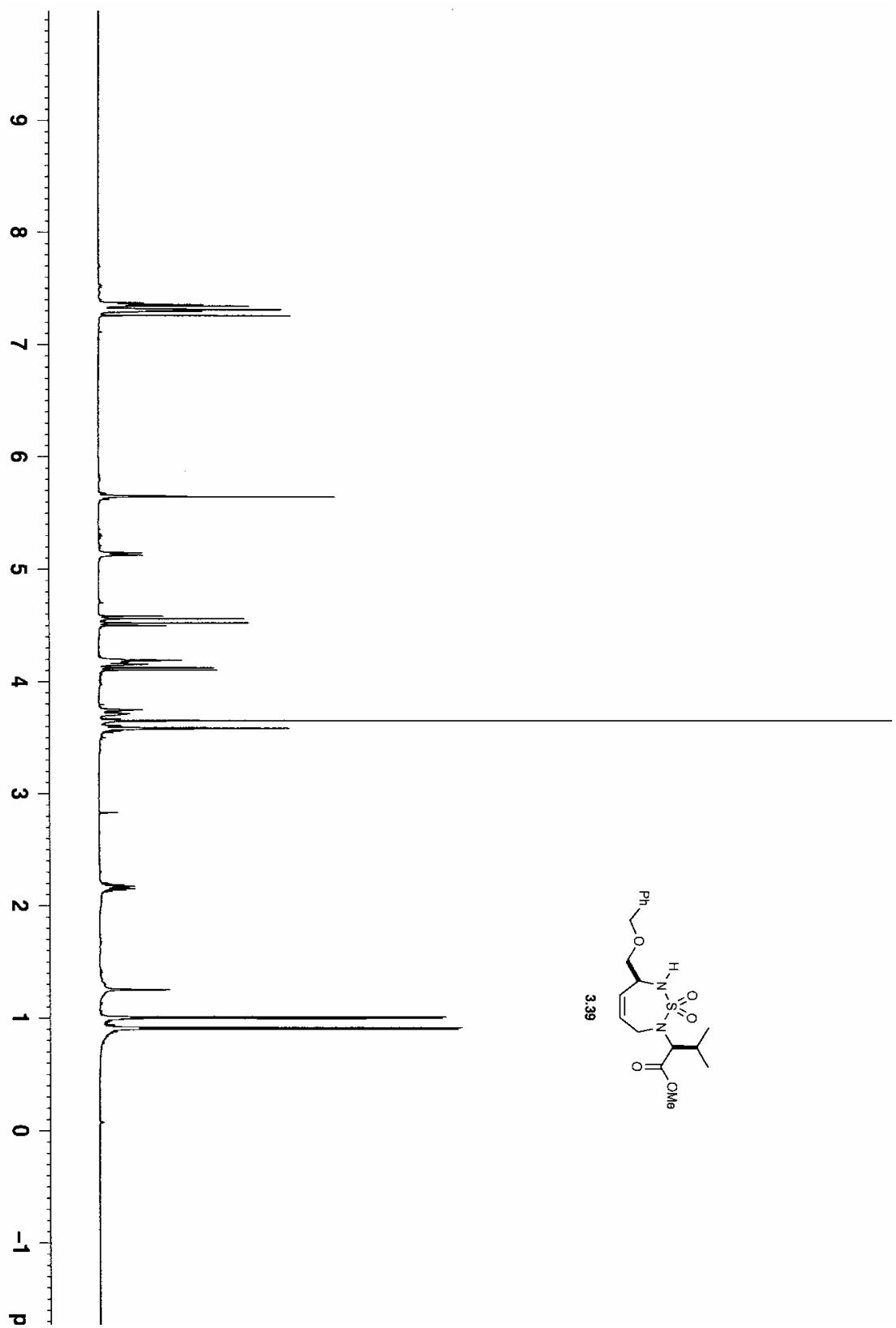
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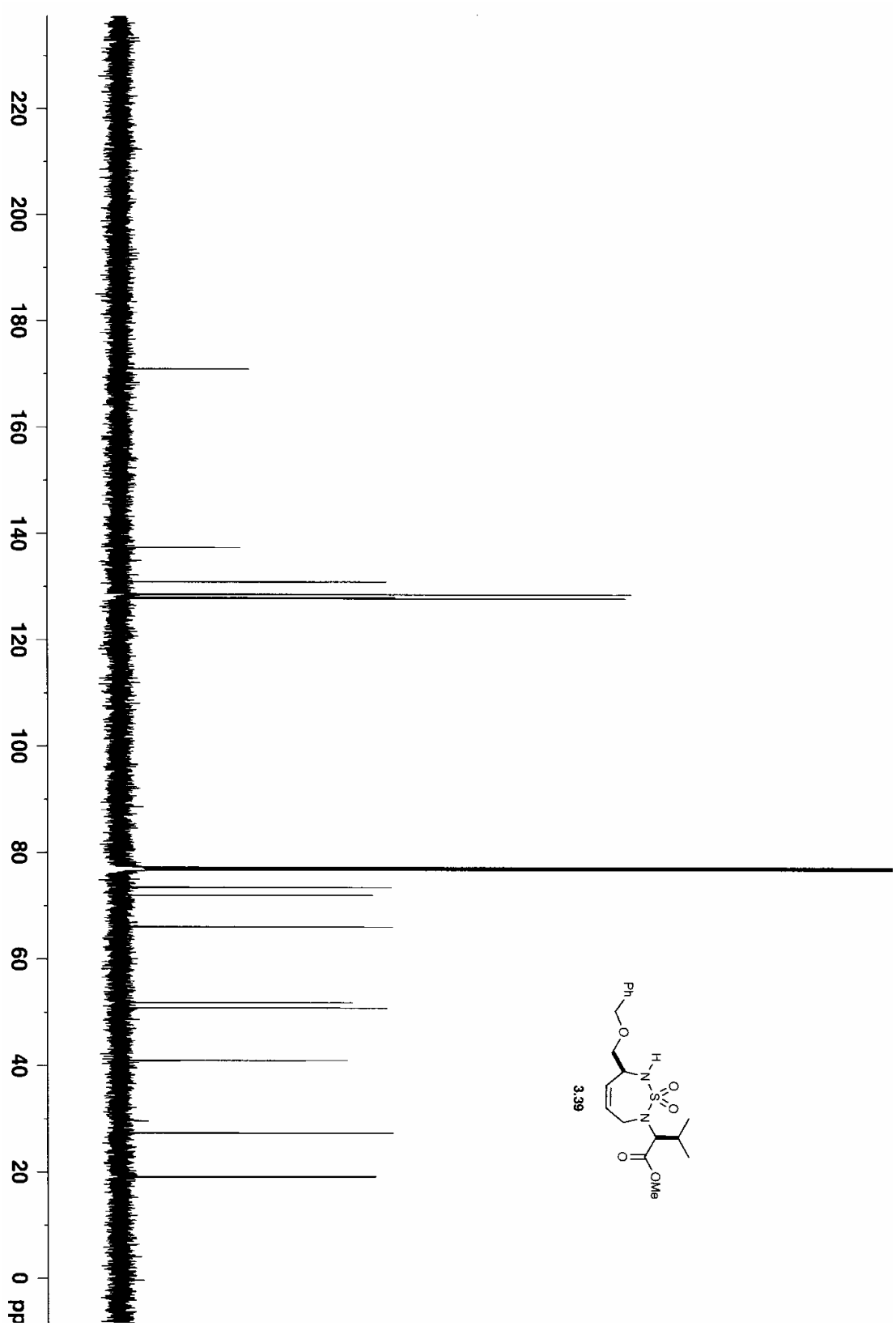
O
OMe
3.39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20
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Ph
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N
S
O
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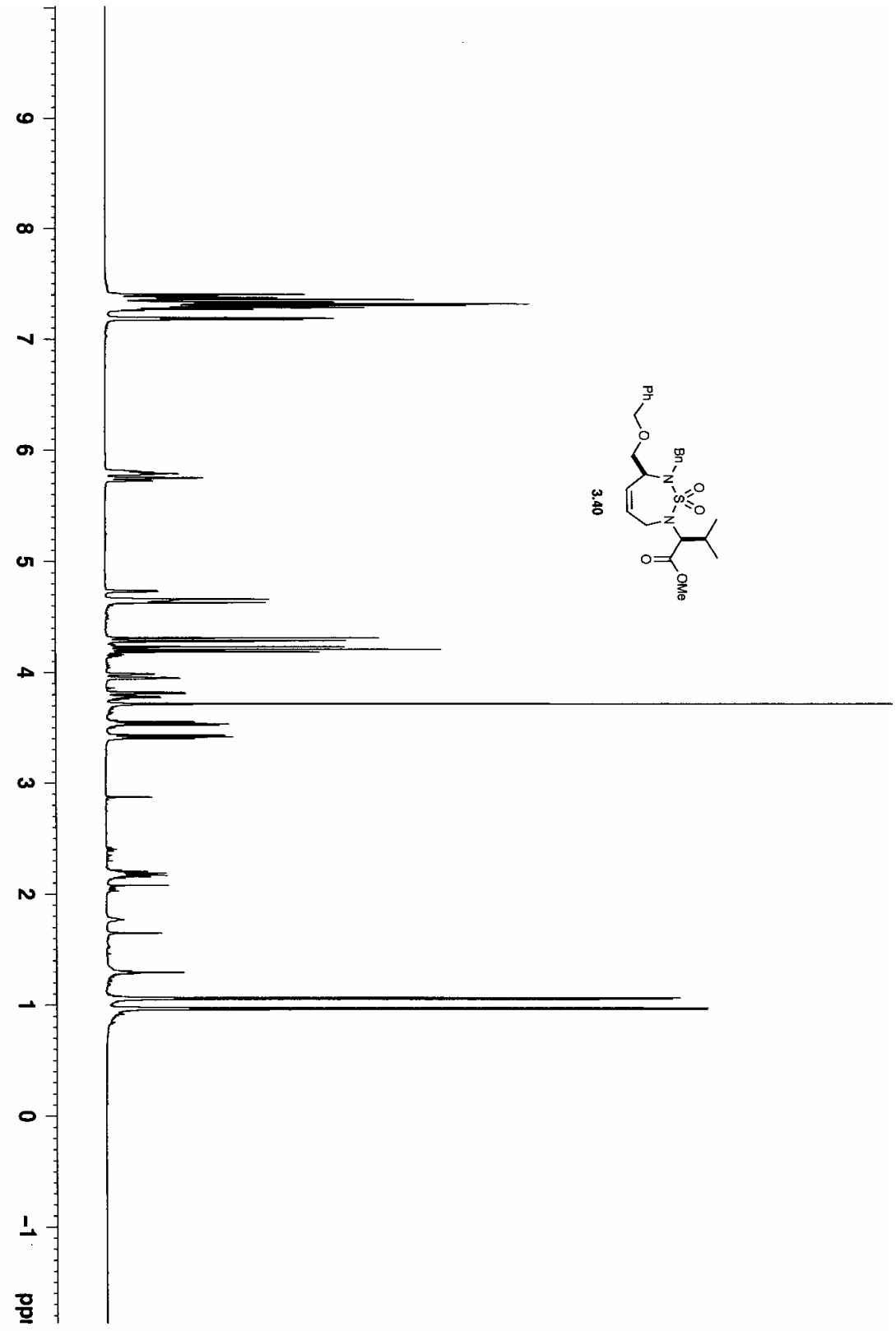
O
OMe
3.39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-1
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Ph
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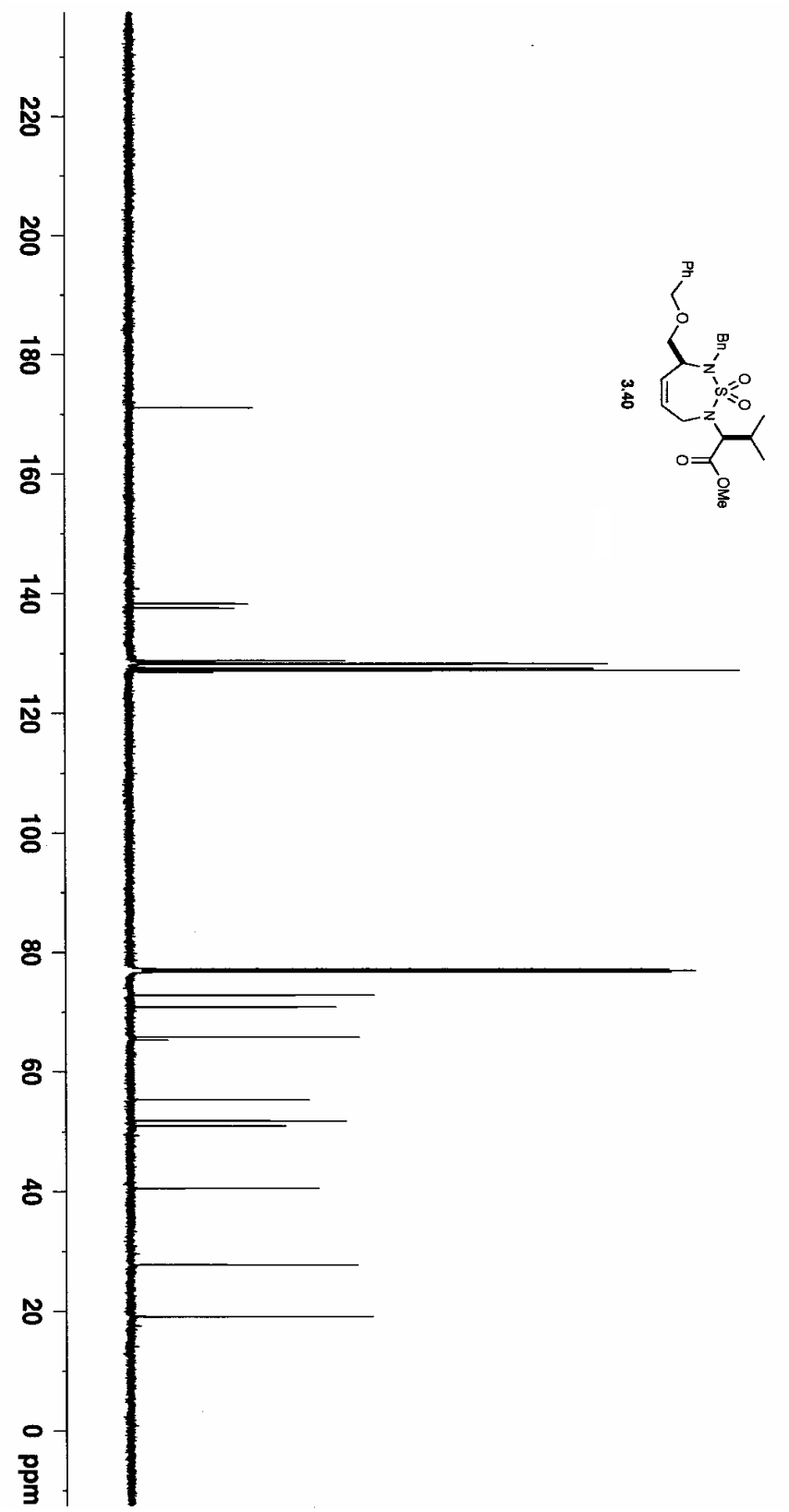
N
O
OMe
3.40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20
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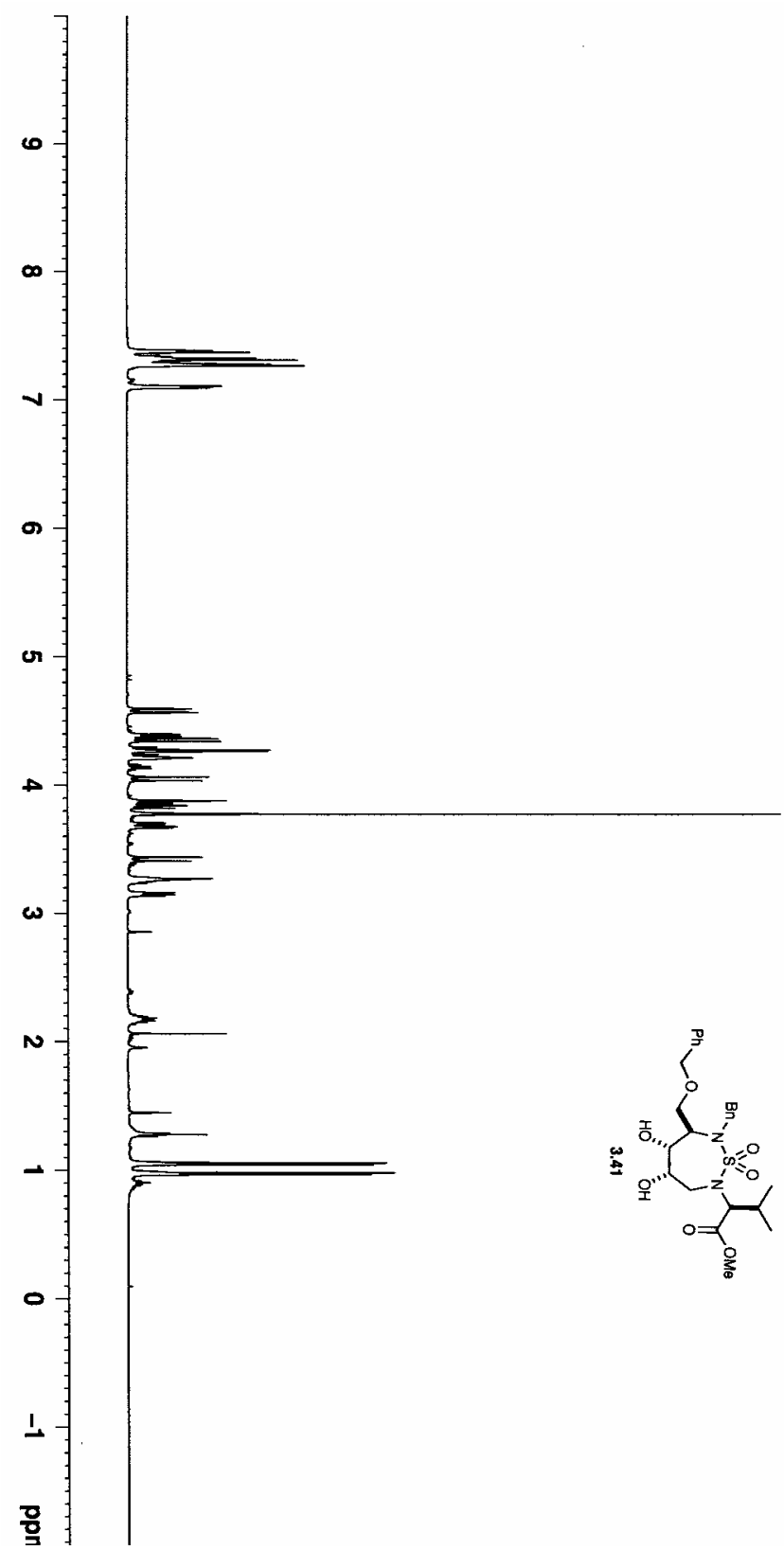
O
N
O
OMe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6
5
4
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2
1
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−1
ppm
Ph
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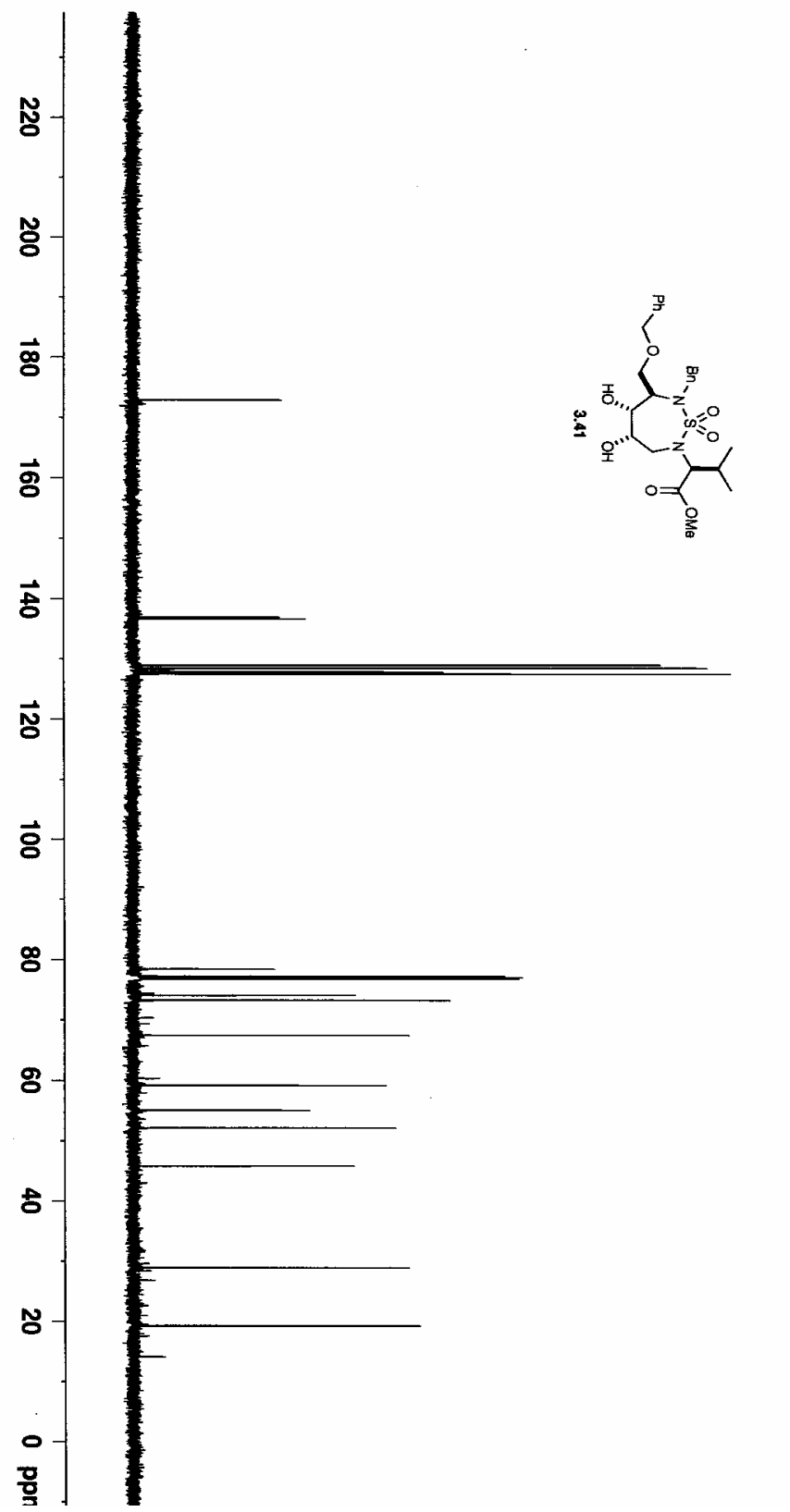
Bn
N
S
O
O
N
HO
OH
O
OMe
3.41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120
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60
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20
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Ph
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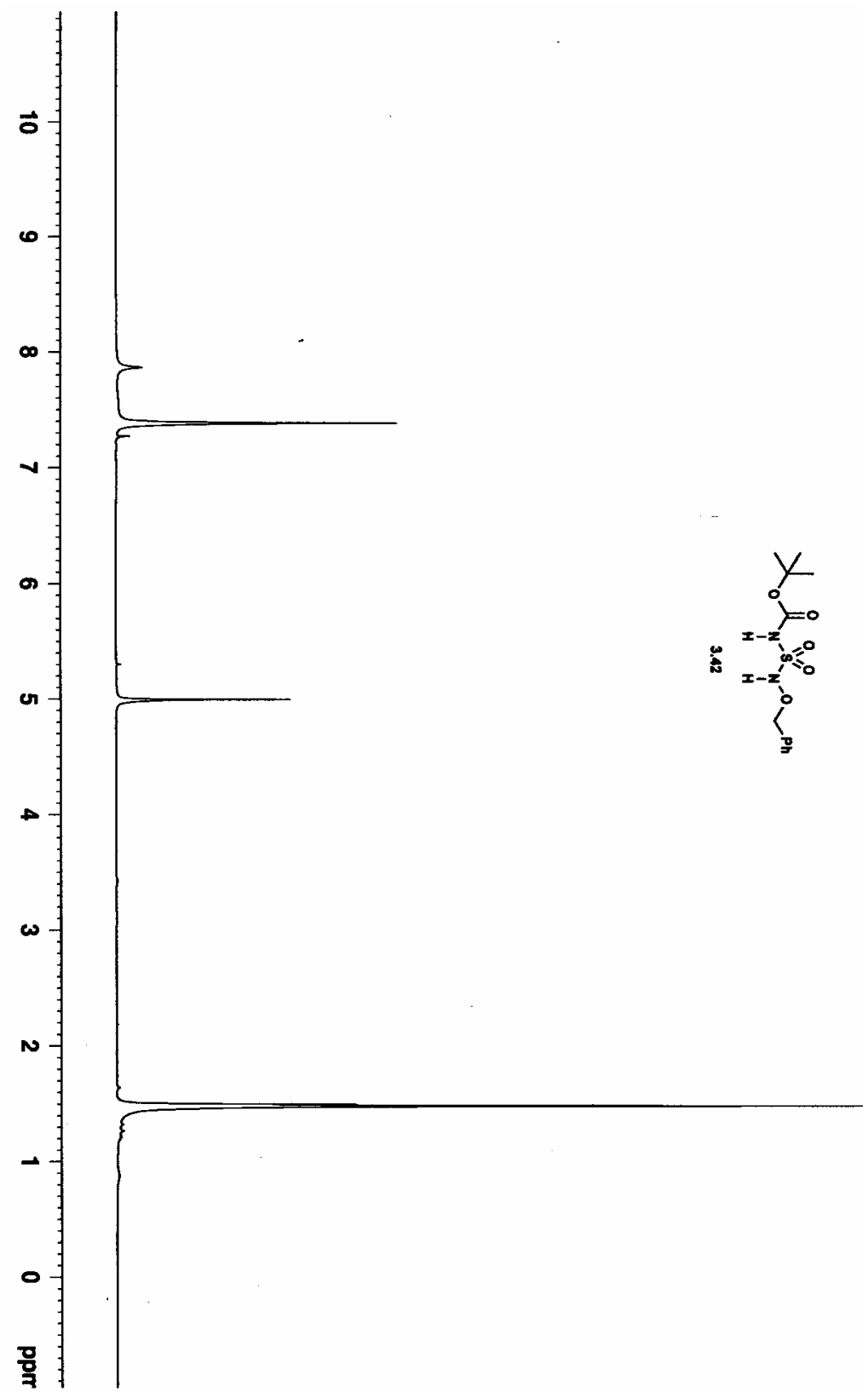
Bn
N
S
O
O
N
HO
OH
3.41
O
OMe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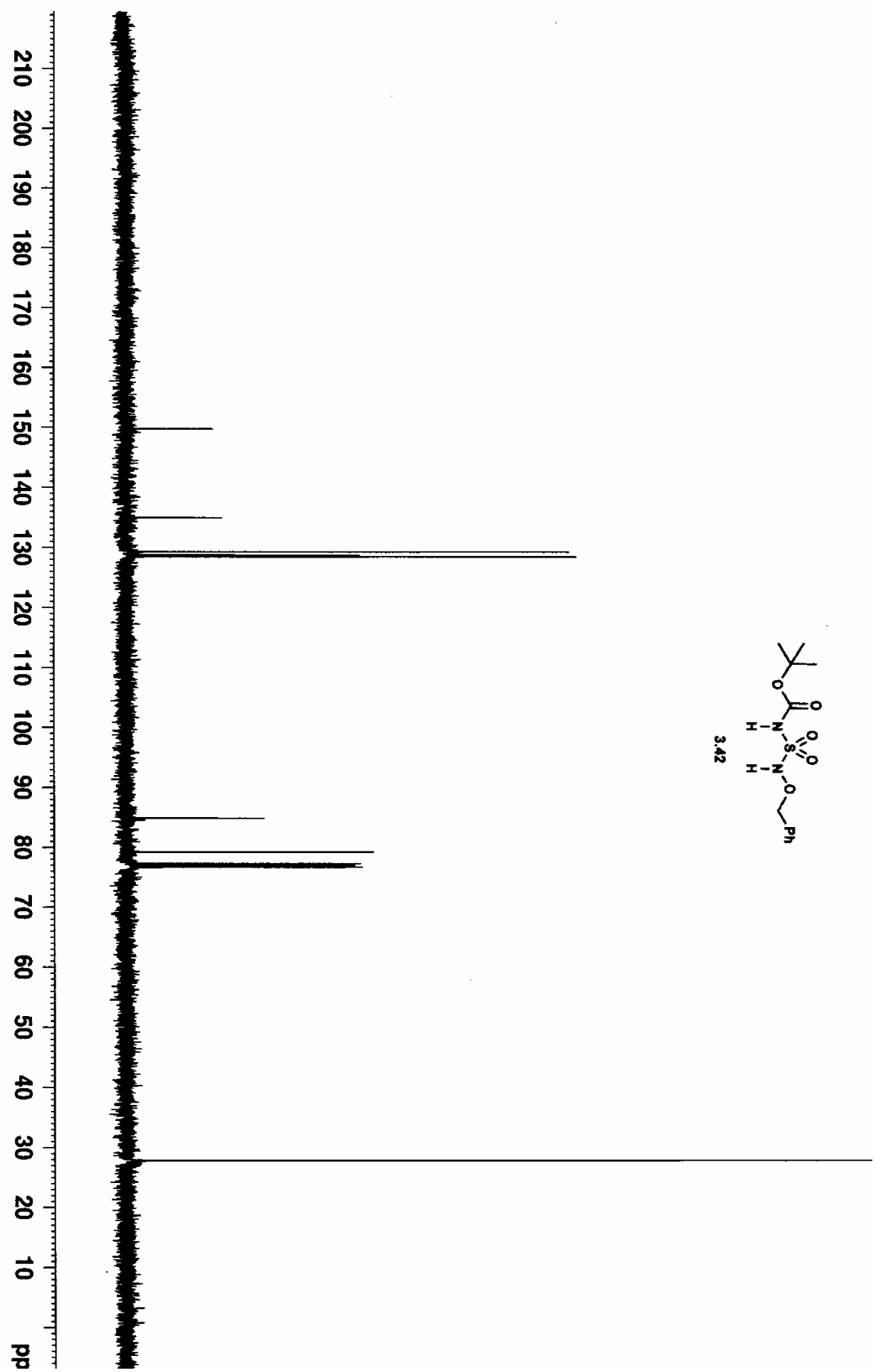
6
5
4
3
2
1
0
ppm
3.42
Ph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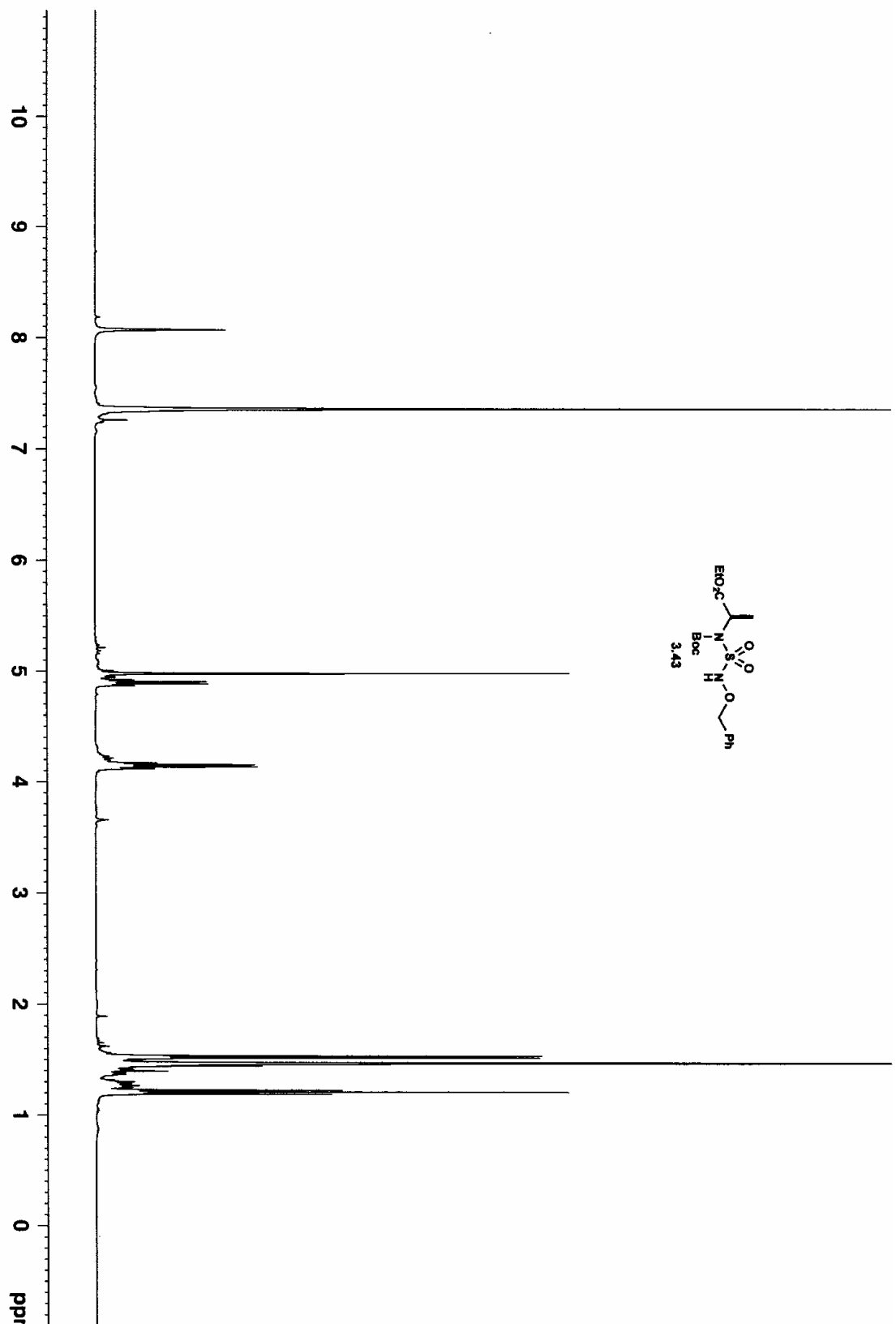
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ppr
EtO2C
N
Boc
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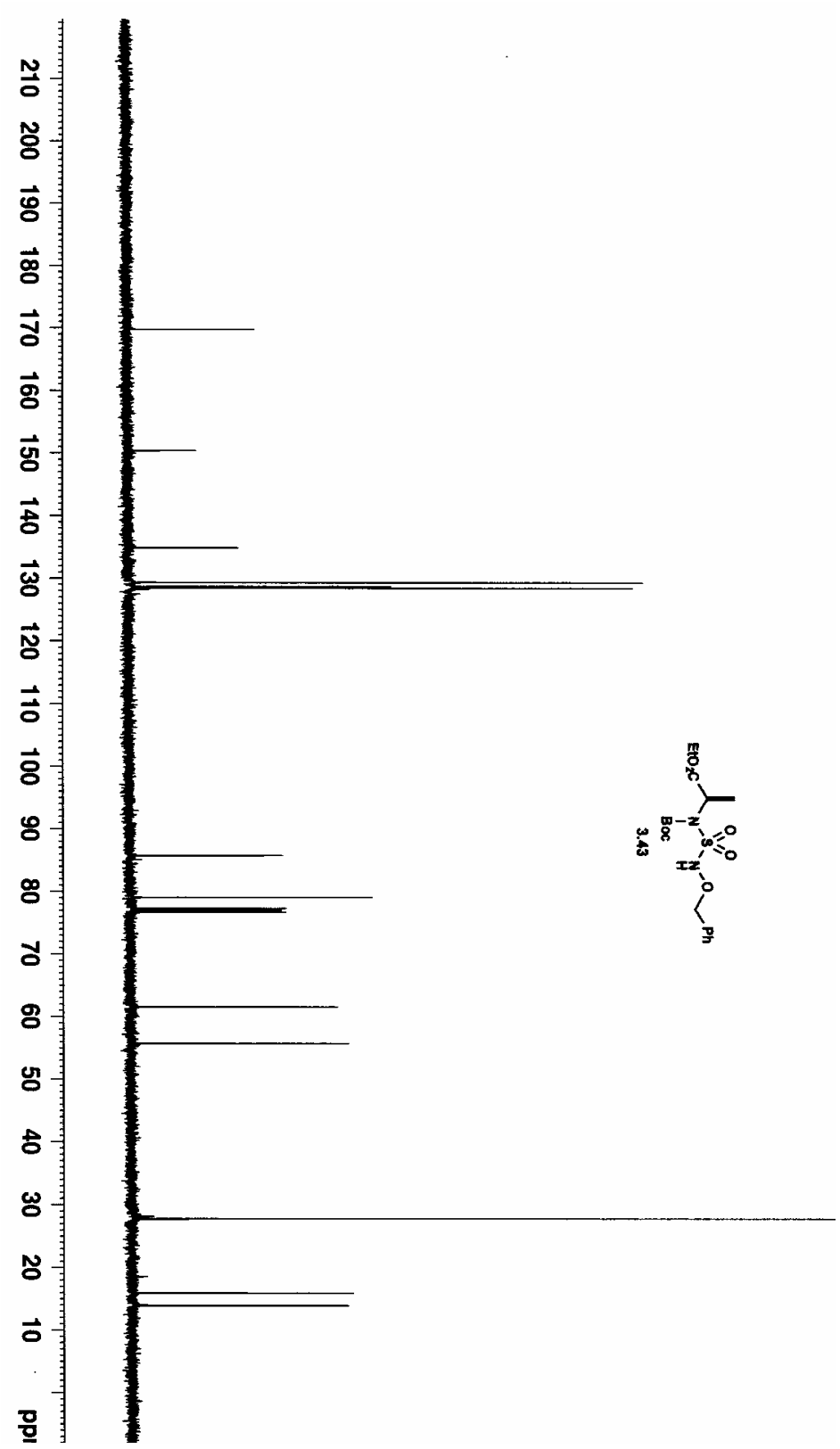
S
N
H
O
Ph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110
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90
80
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20
10
ppm
EtO2C
N
Boc
3.43
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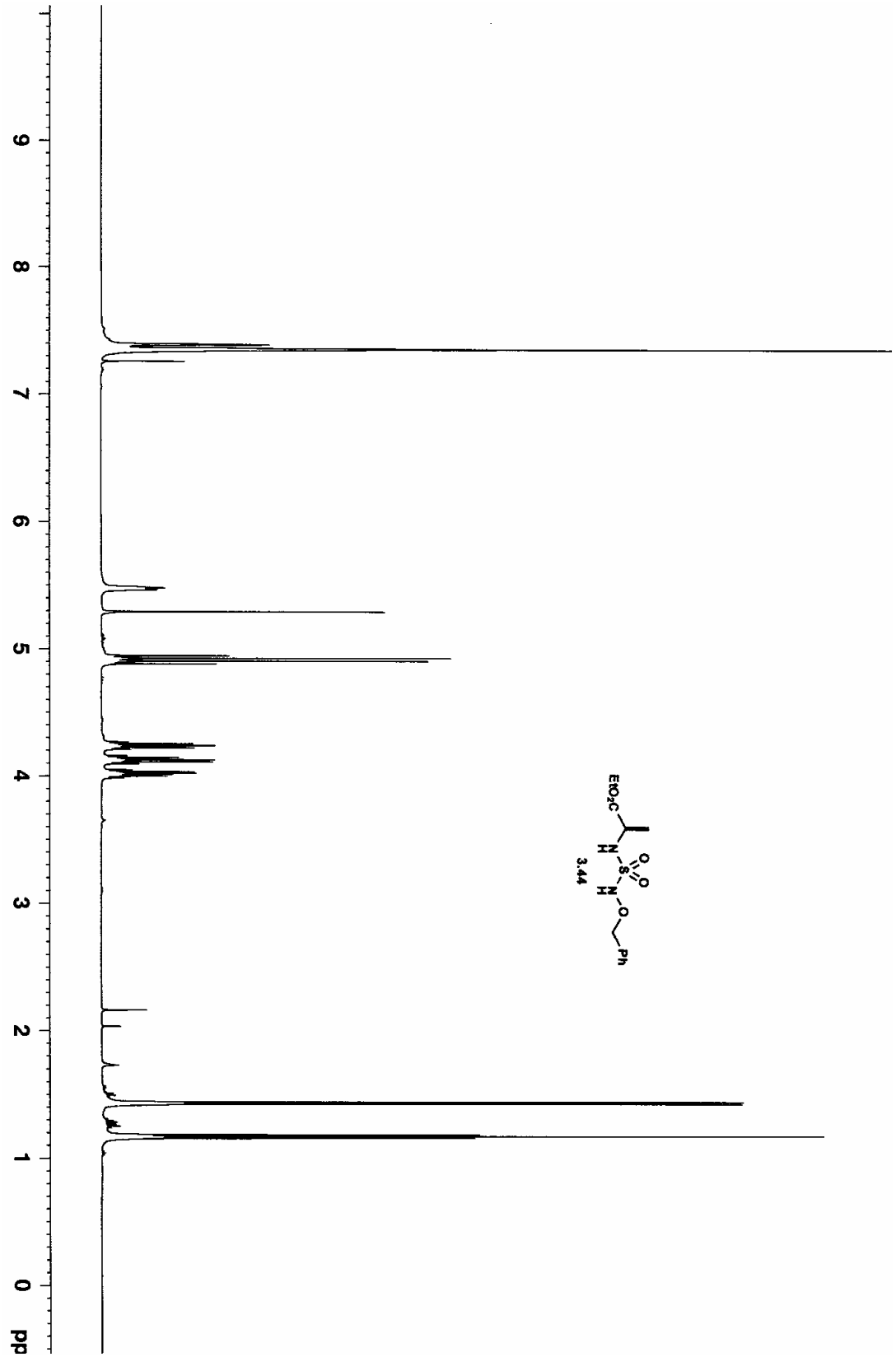
O
S
N
H
O
Ph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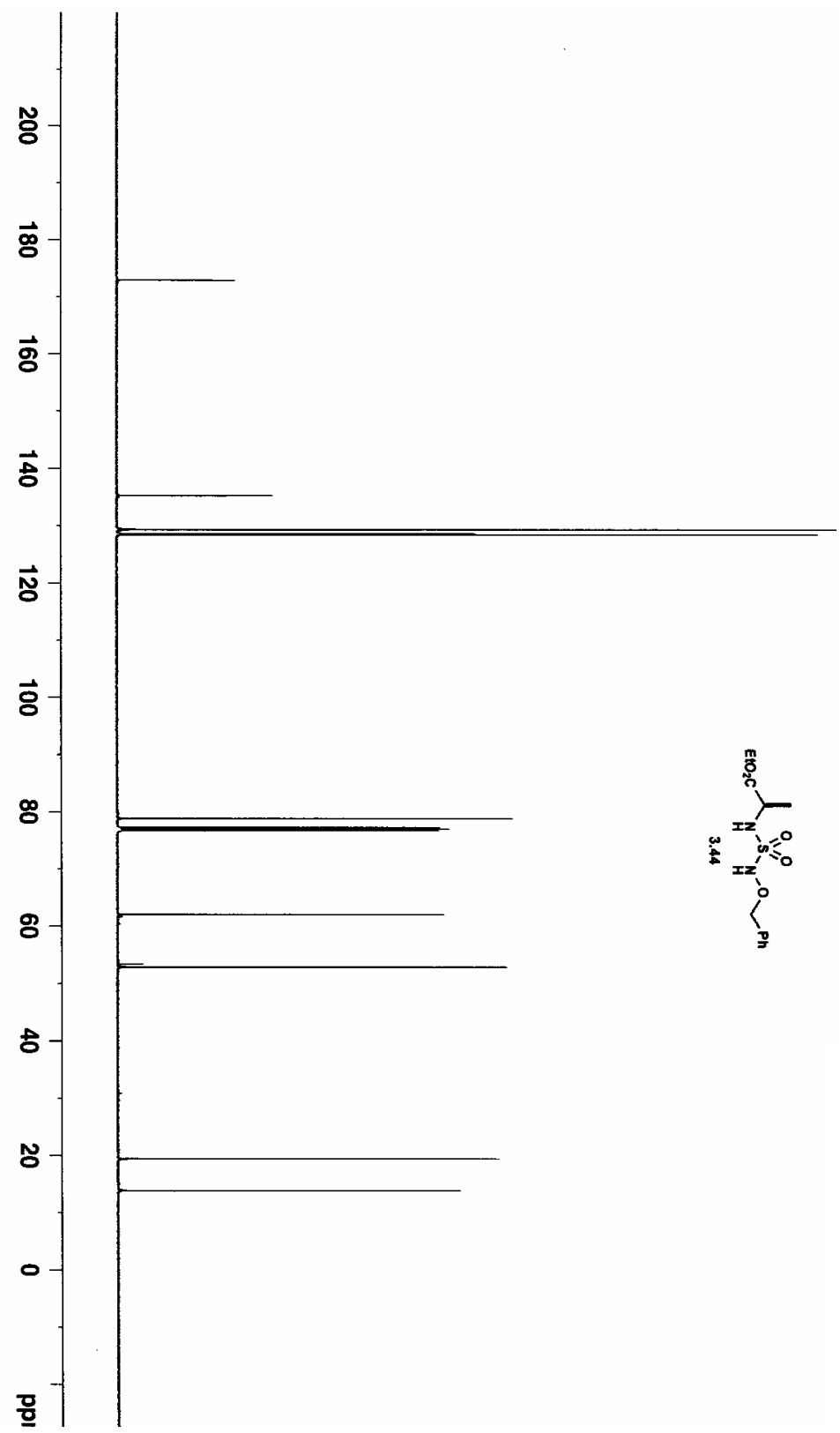
EtO2C
Ph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S
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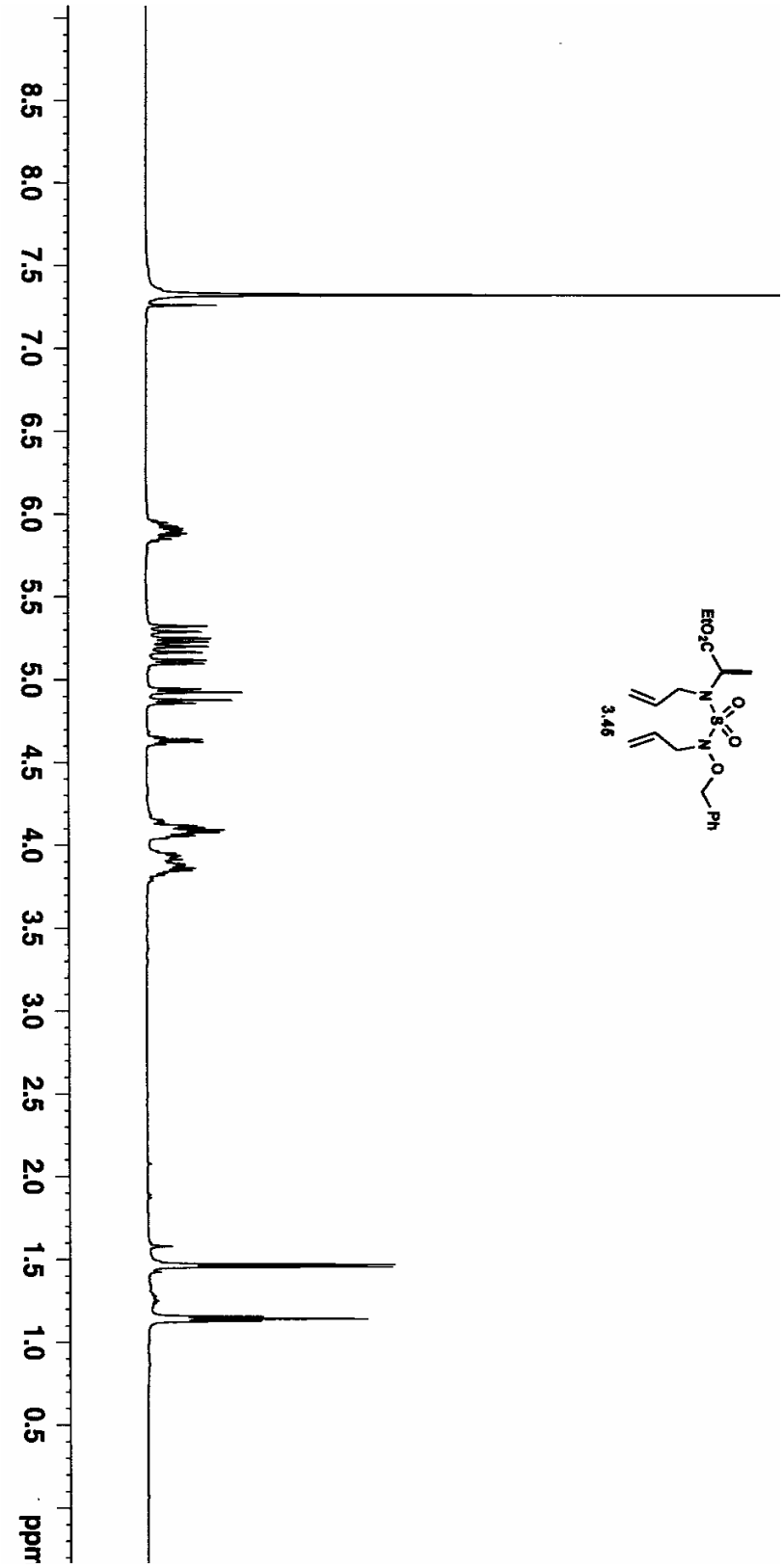
N
O
Ph
3.44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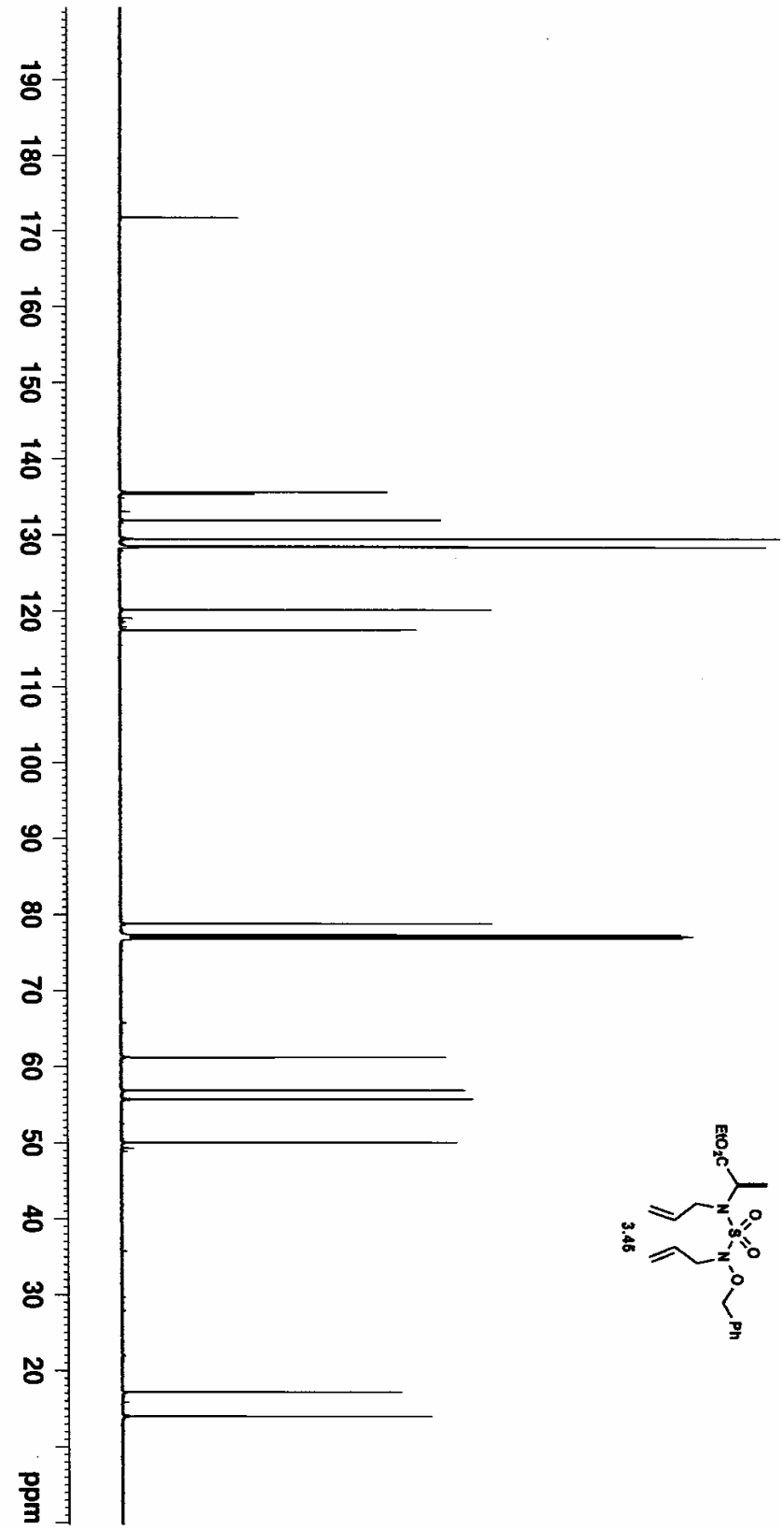
ppm
3.46
EtO2C
Ph


190
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ppm
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N
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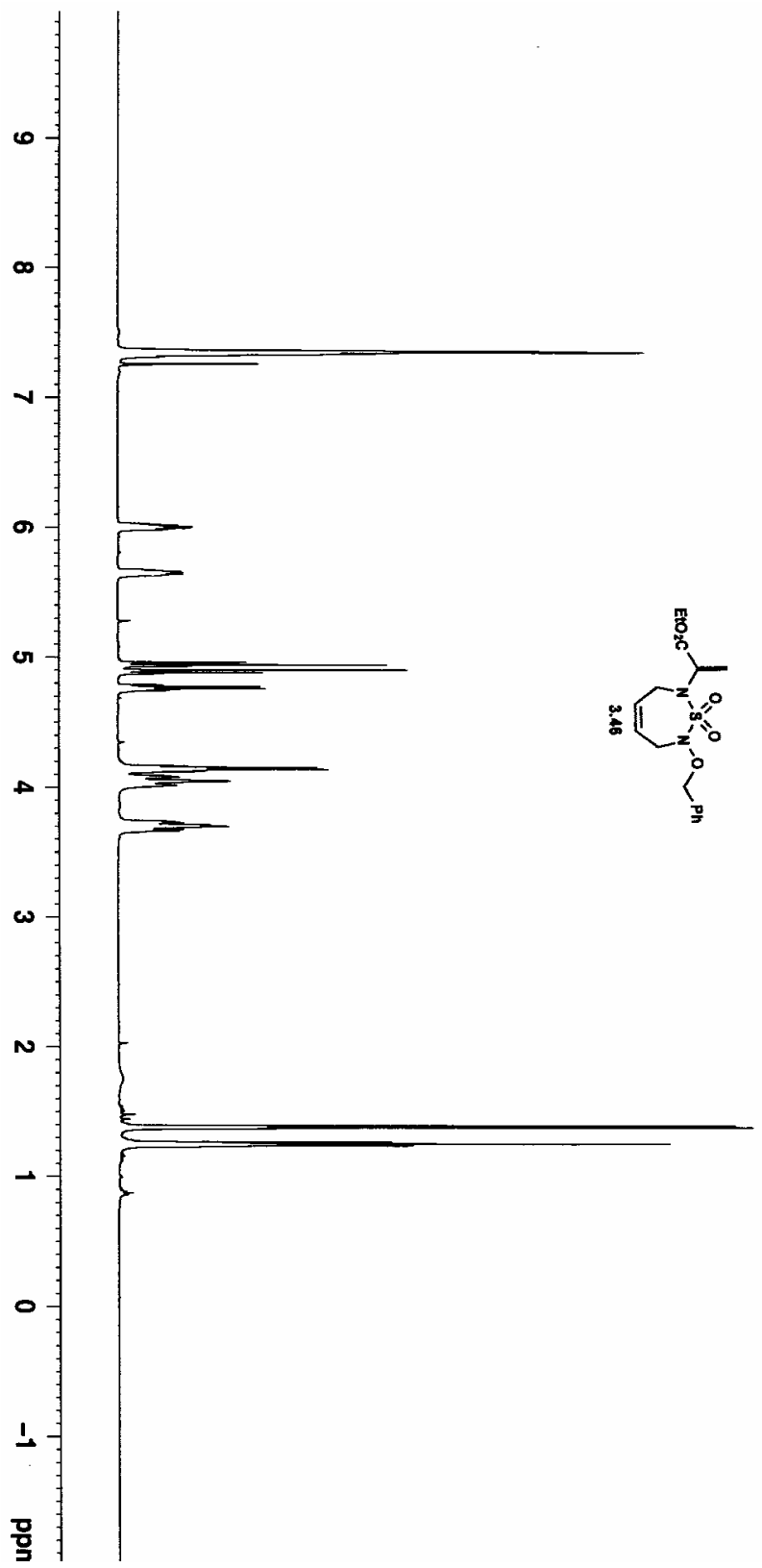
Ph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0
-1
ppm
EtO2C
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S
O
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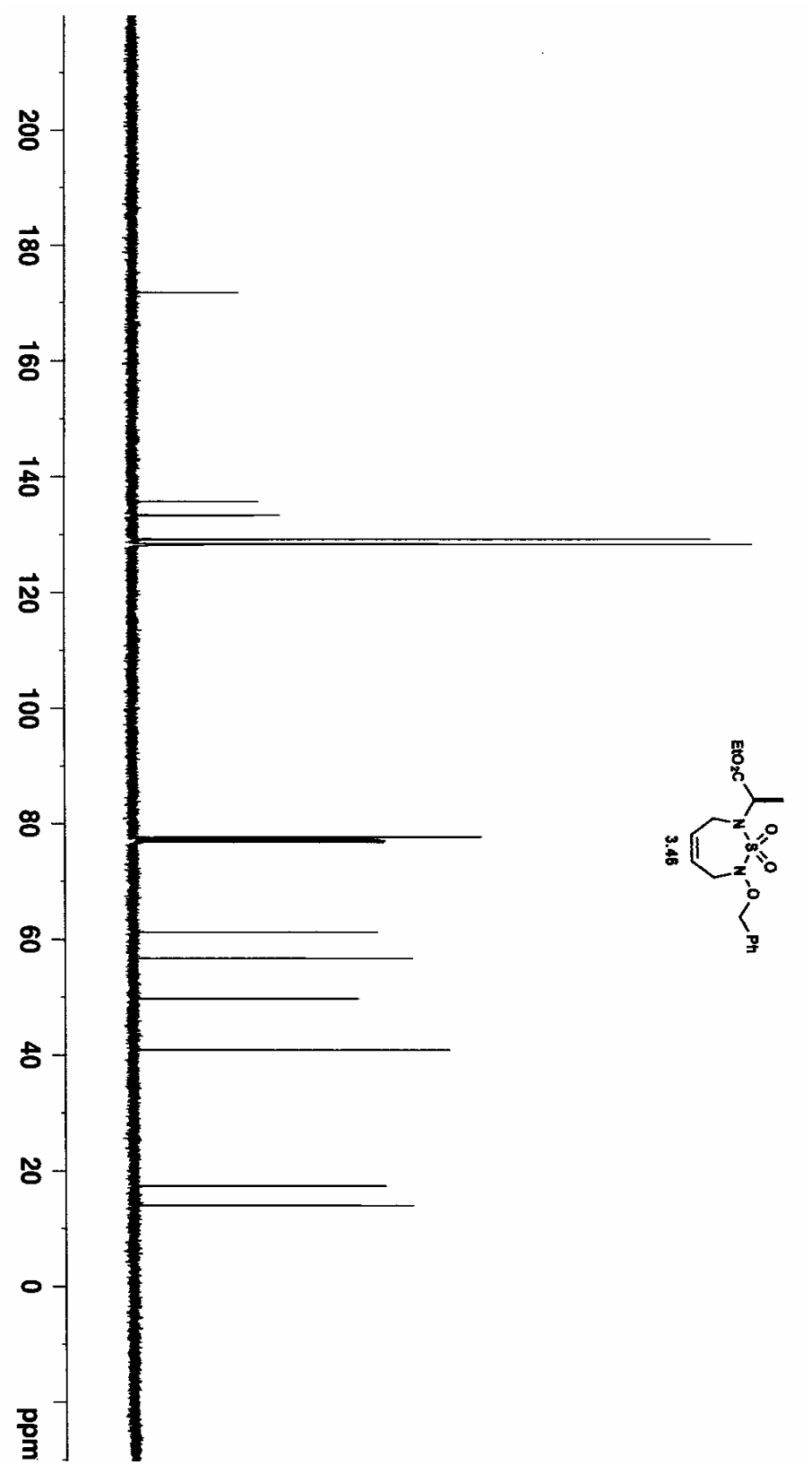
N
O
Ph
3.46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S
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N
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Ph
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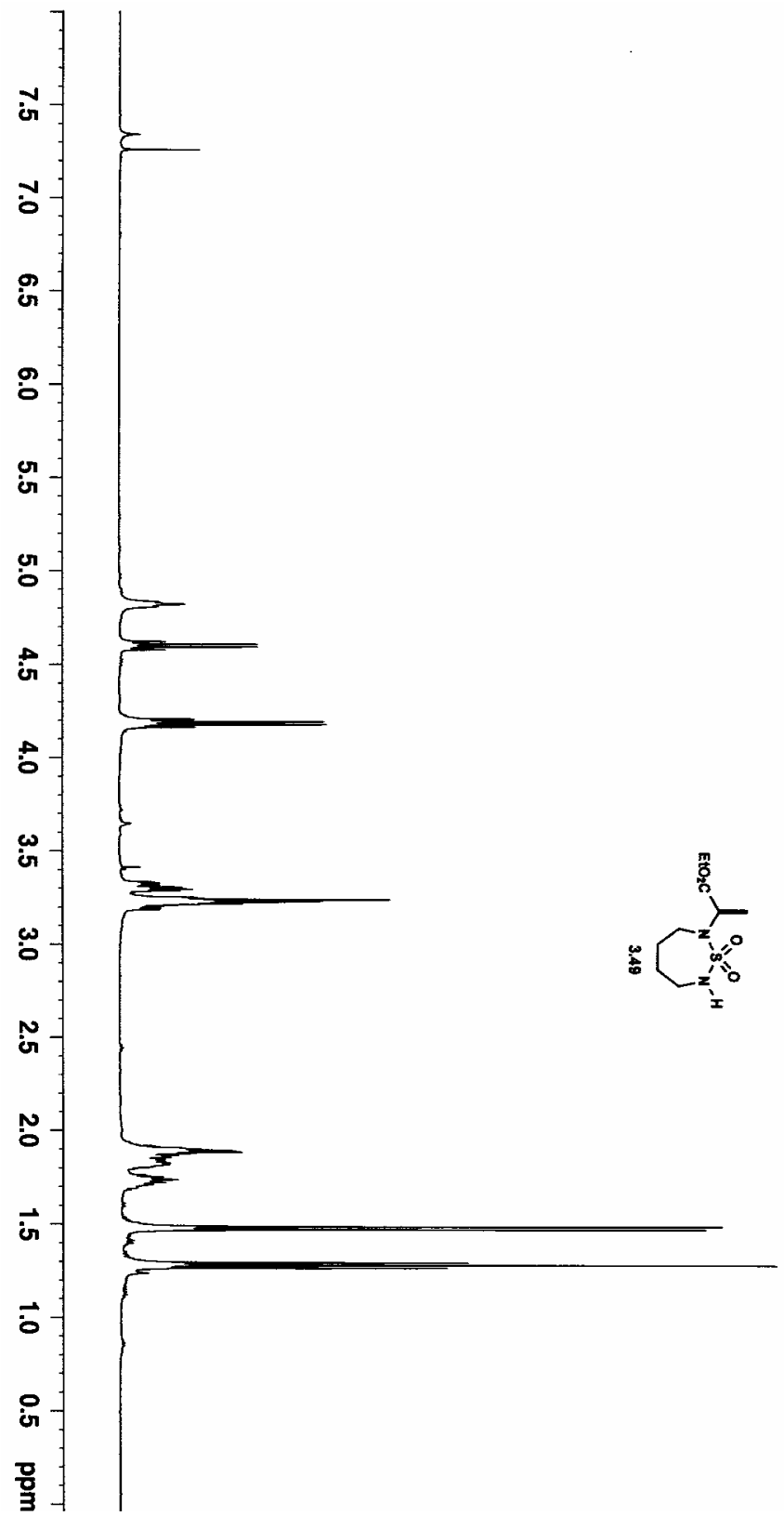
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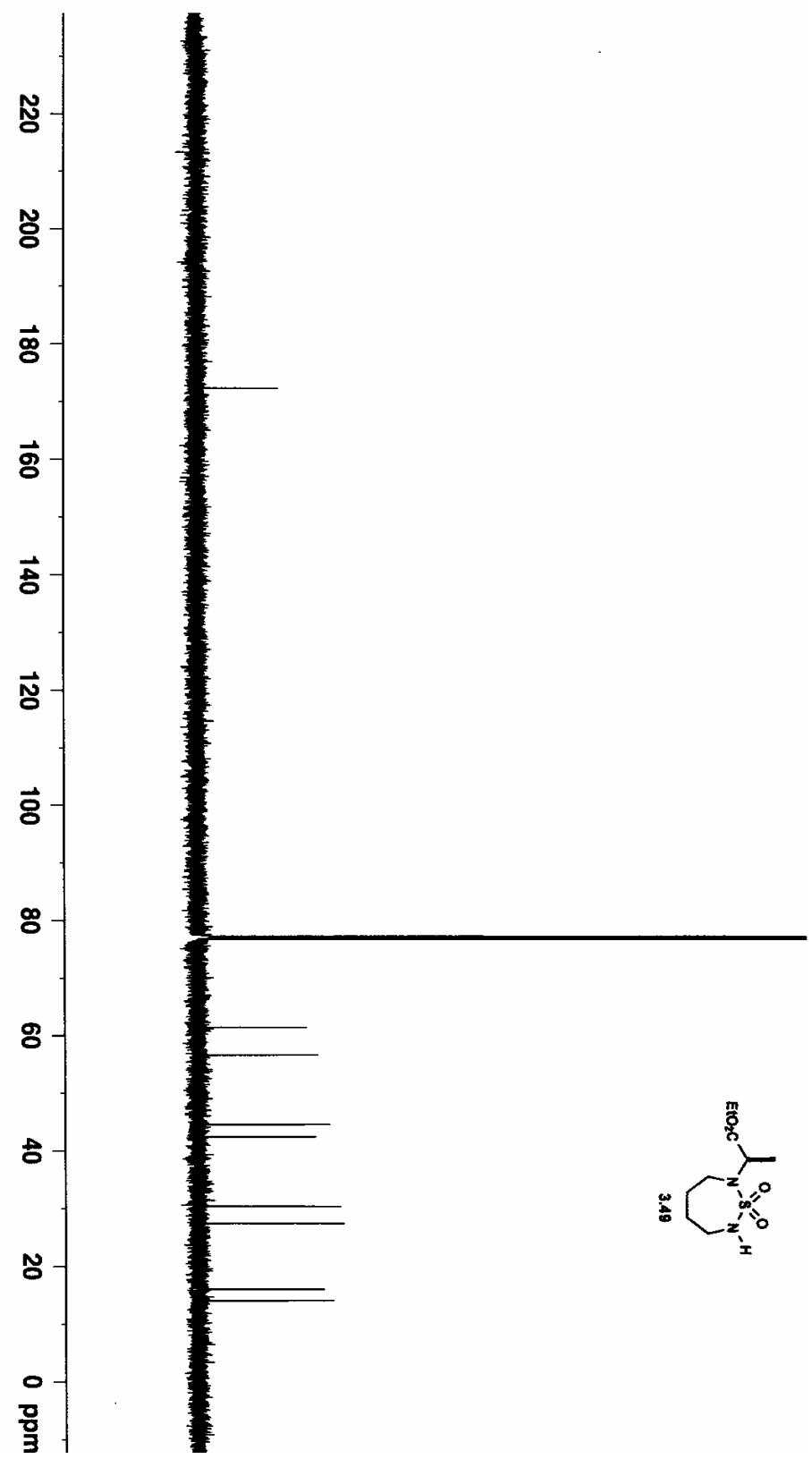
ppm
3.49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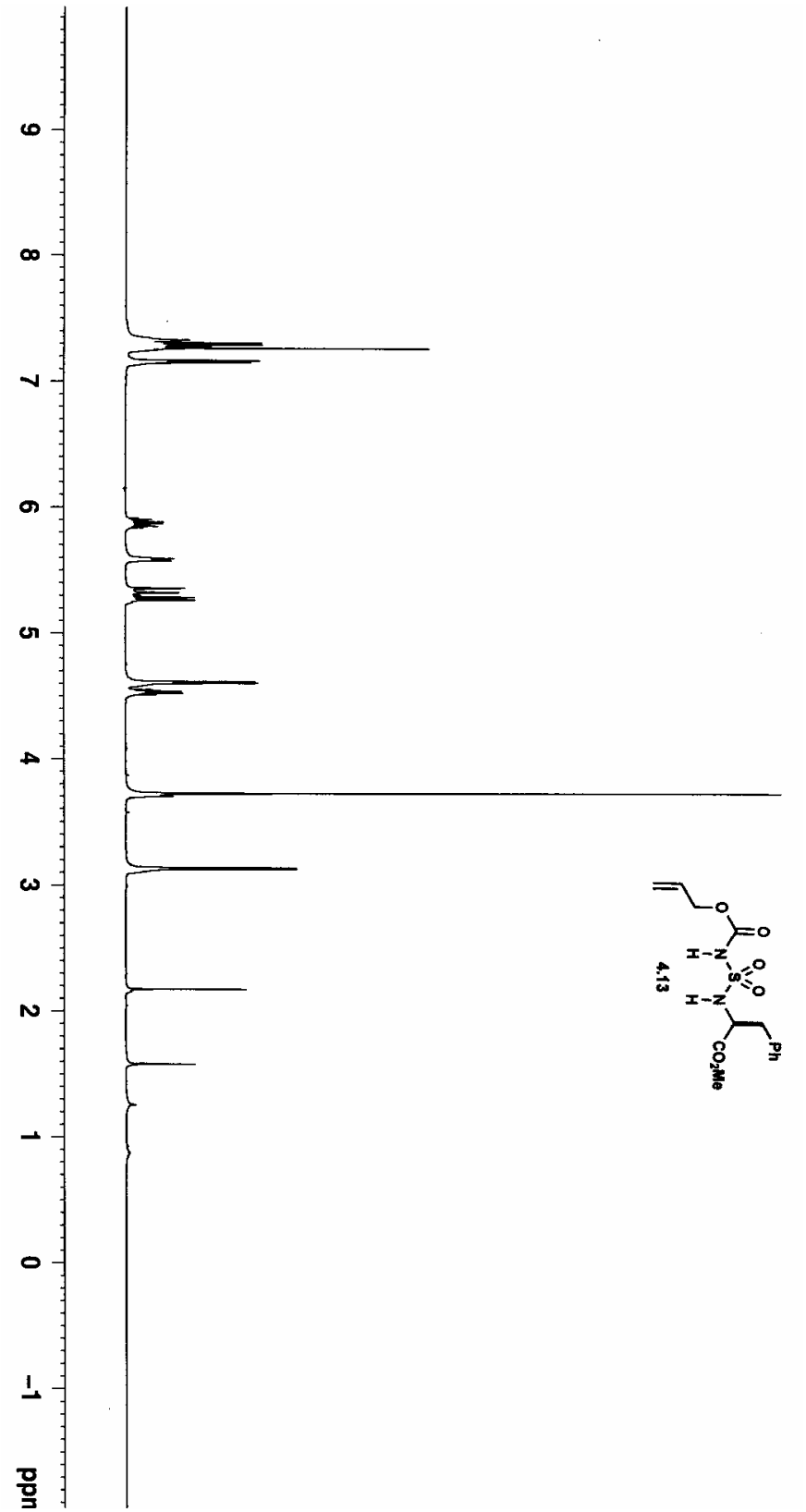
3.49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ppm
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S
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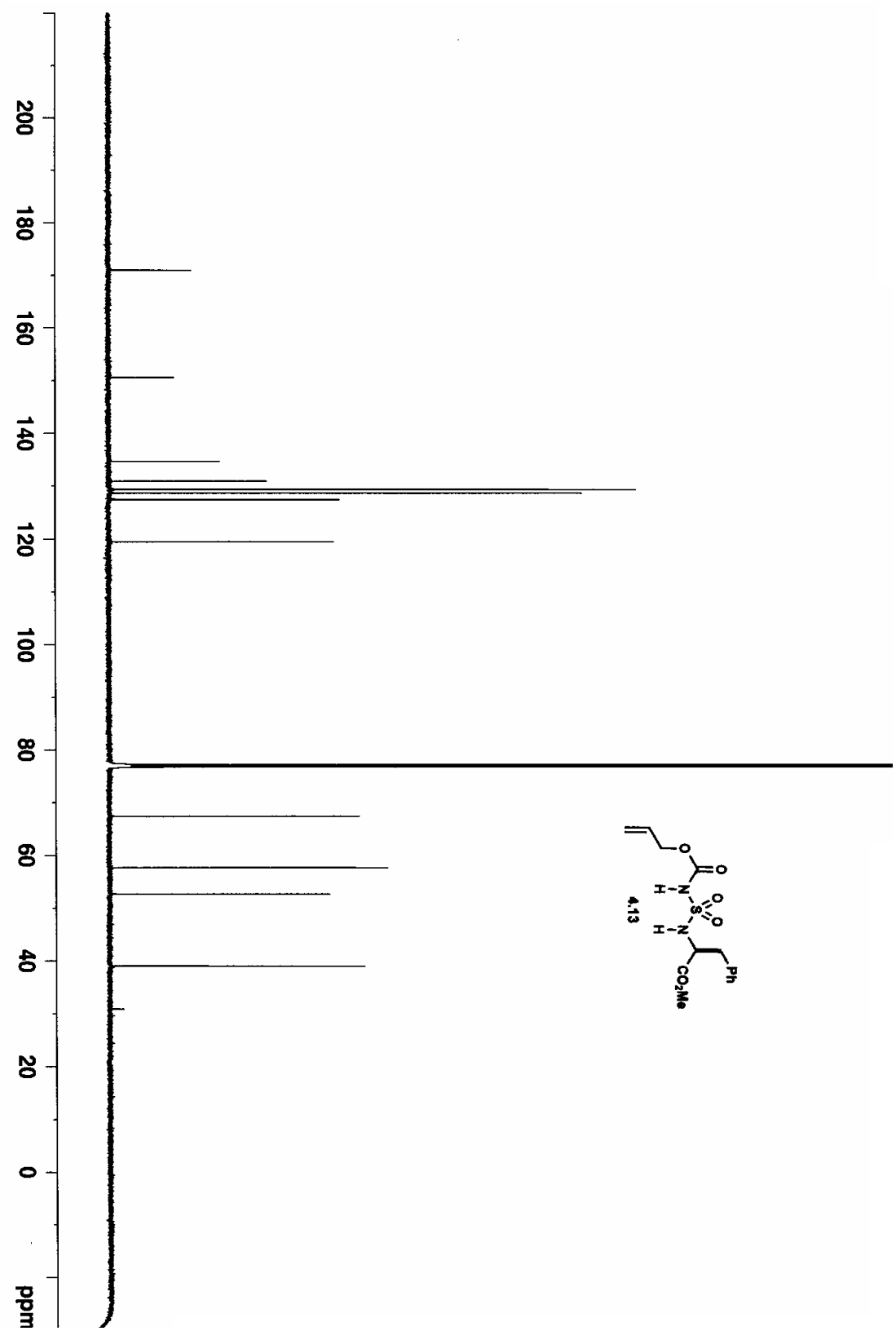
N
H
CO2Me
Ph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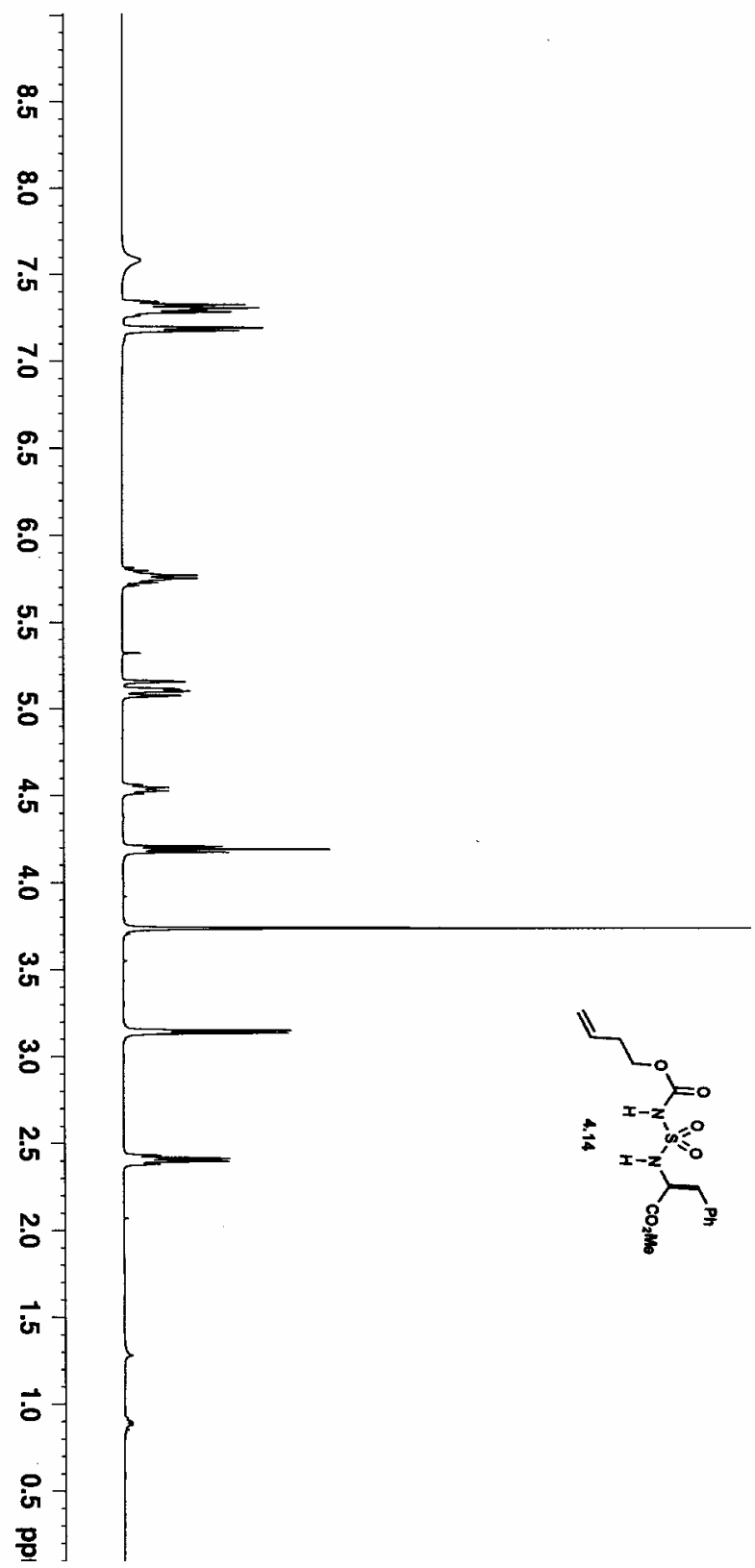
Ph
CO2Me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1.5
1.0
0.5
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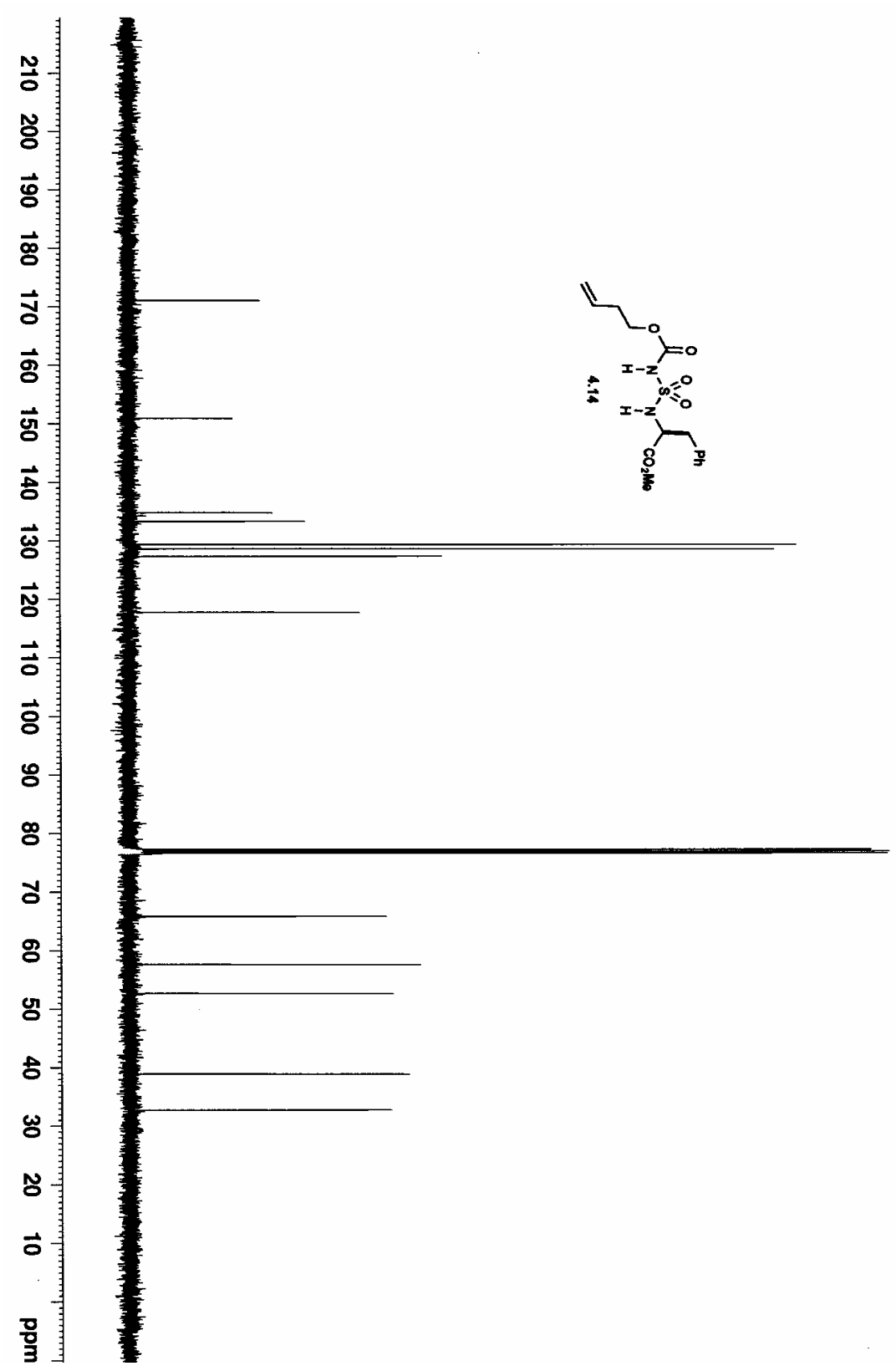
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CO2Me
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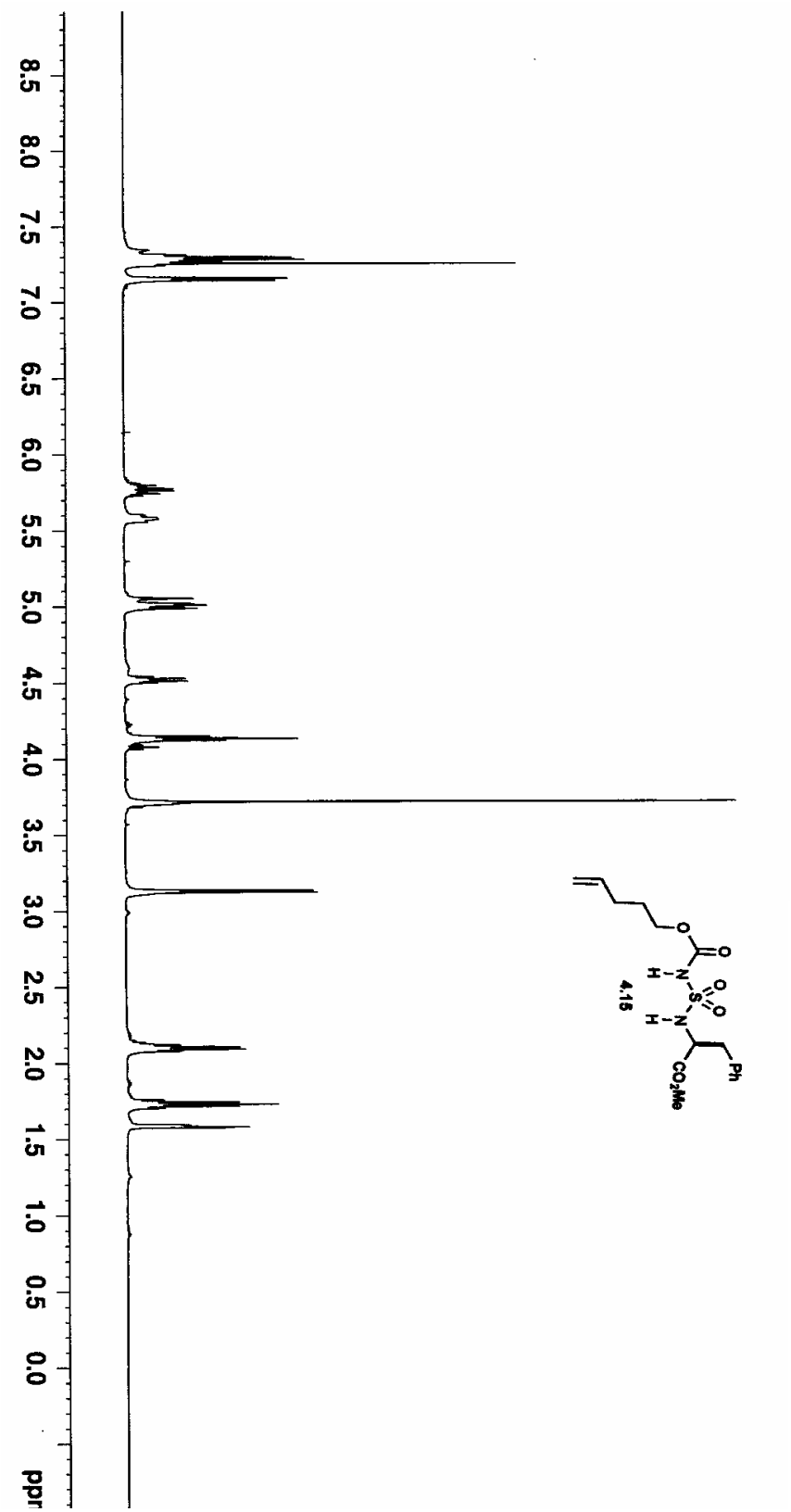
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1.0
0.5
0.0
ppm
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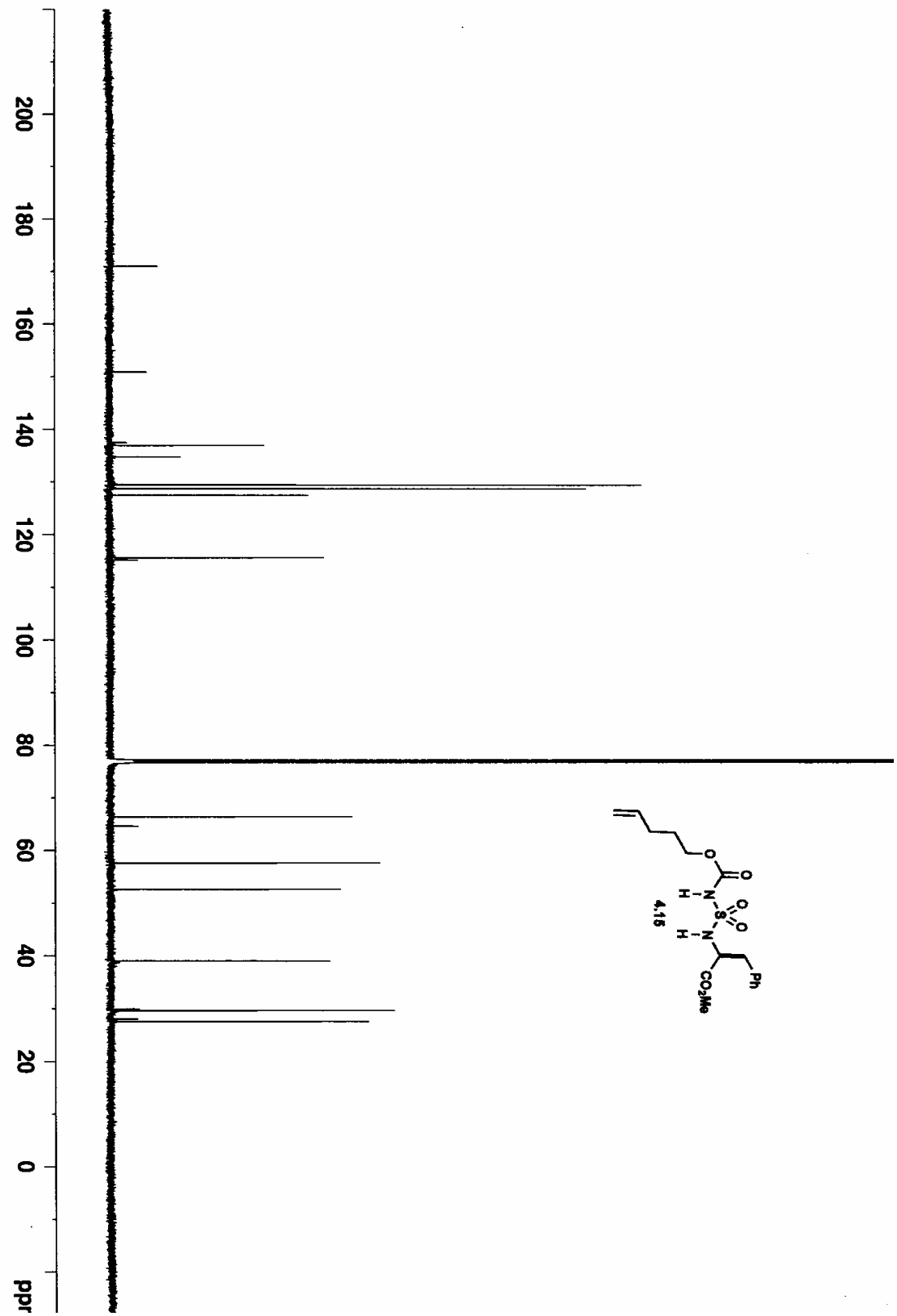
Ph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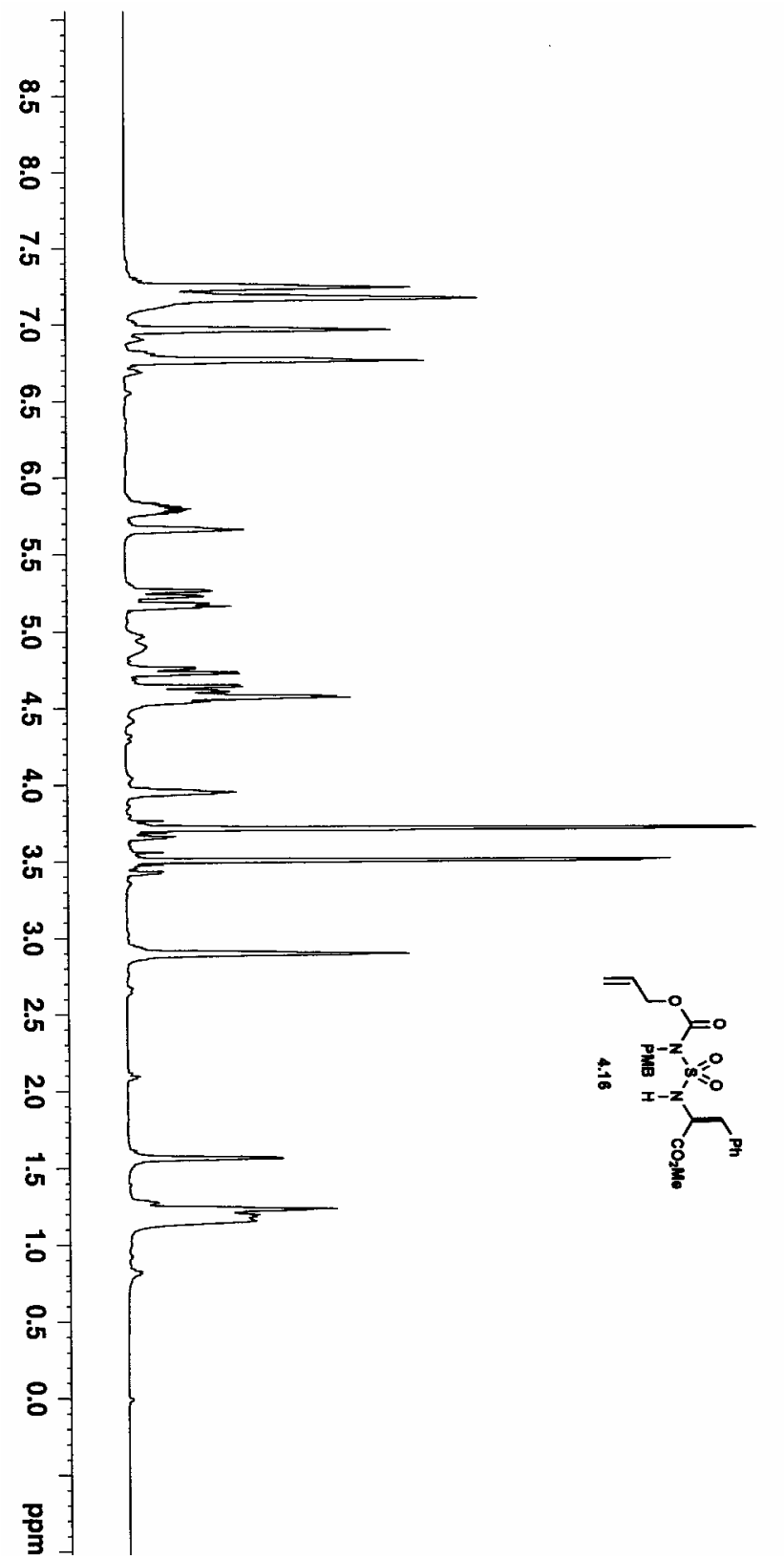
CO2Me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Ph
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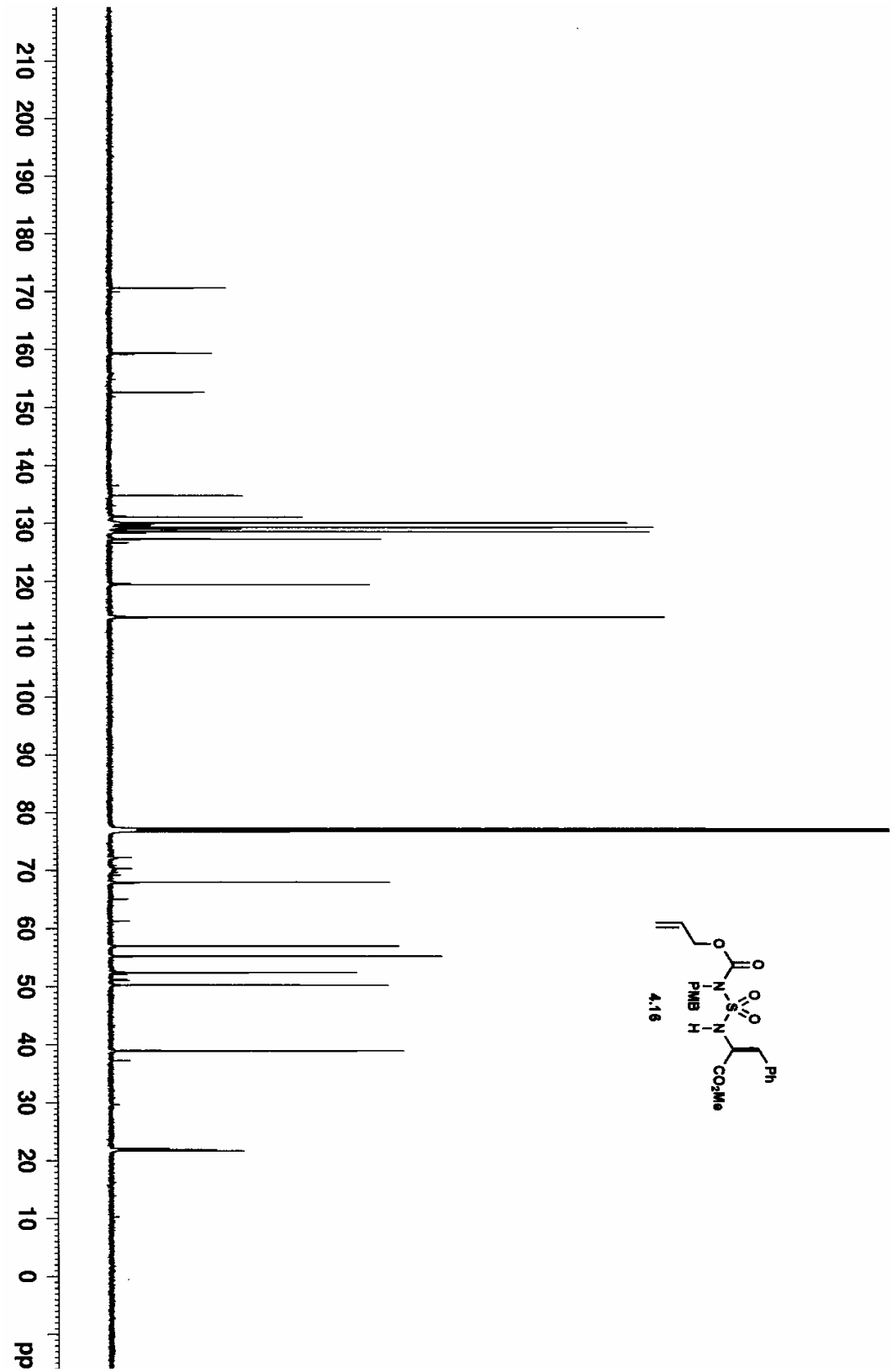
4.16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Ph
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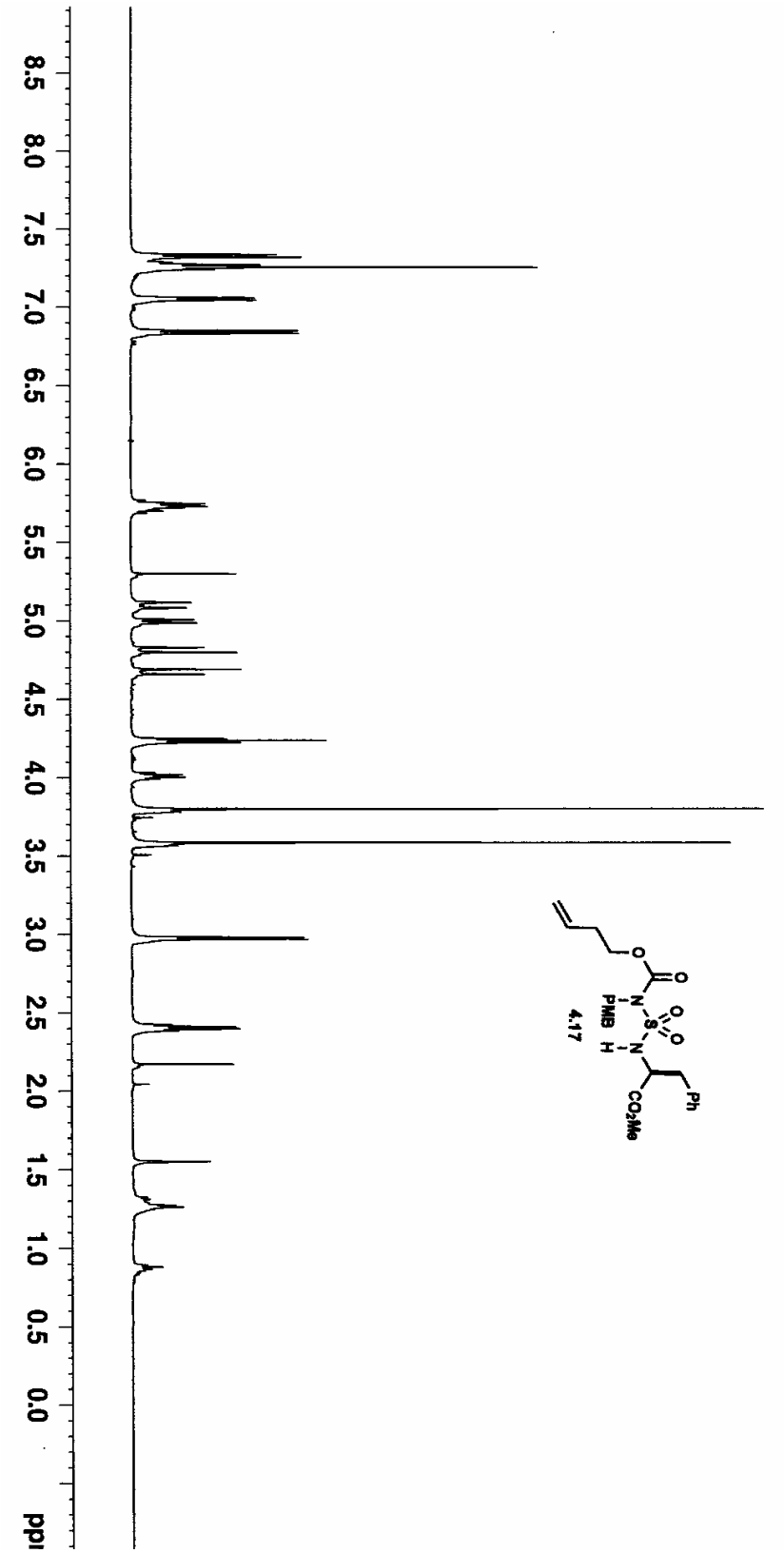
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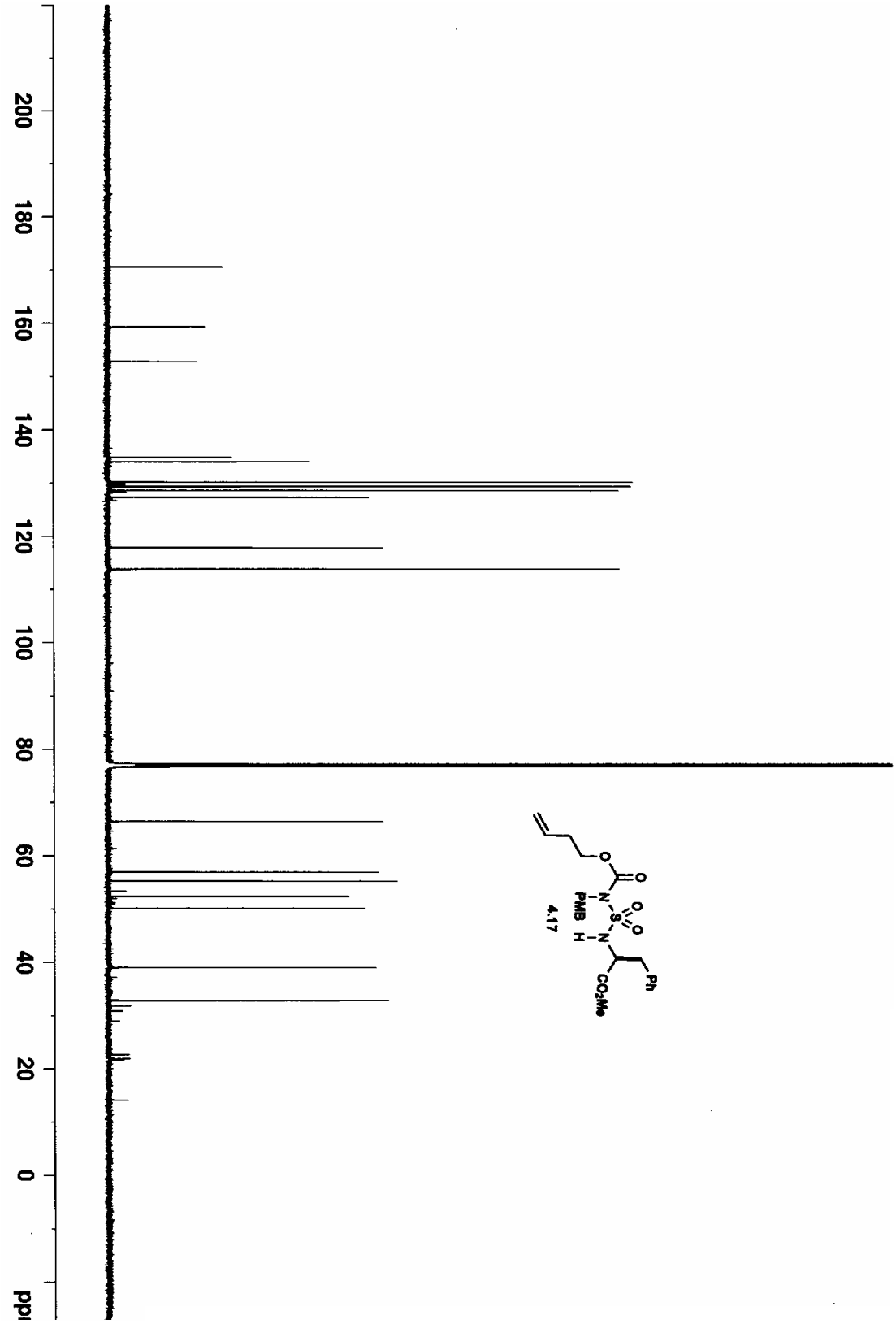
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PMB
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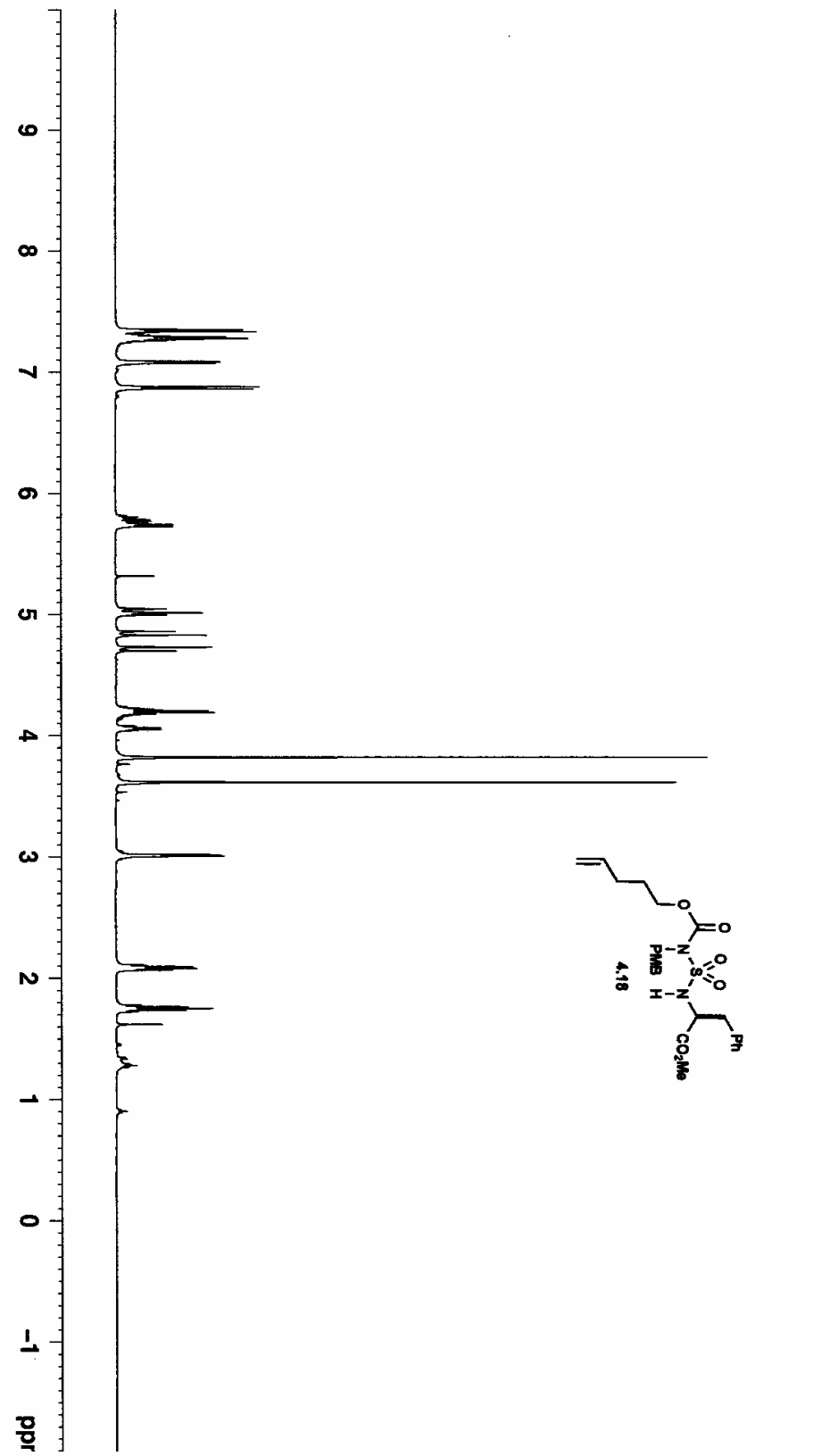
CO2Me
Ph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PMB
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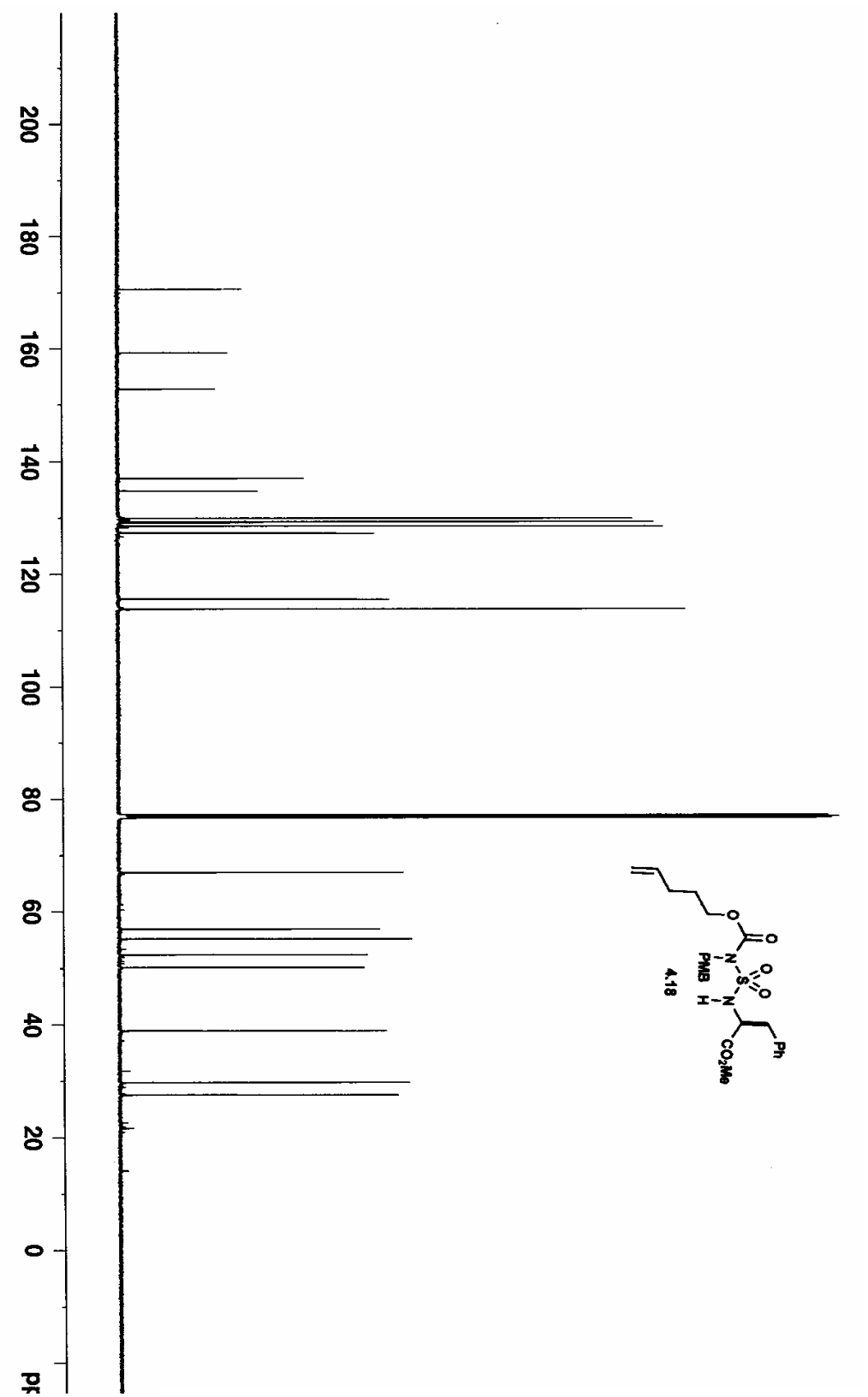
CO2Me
Ph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PF
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PMB
H
CO2Me
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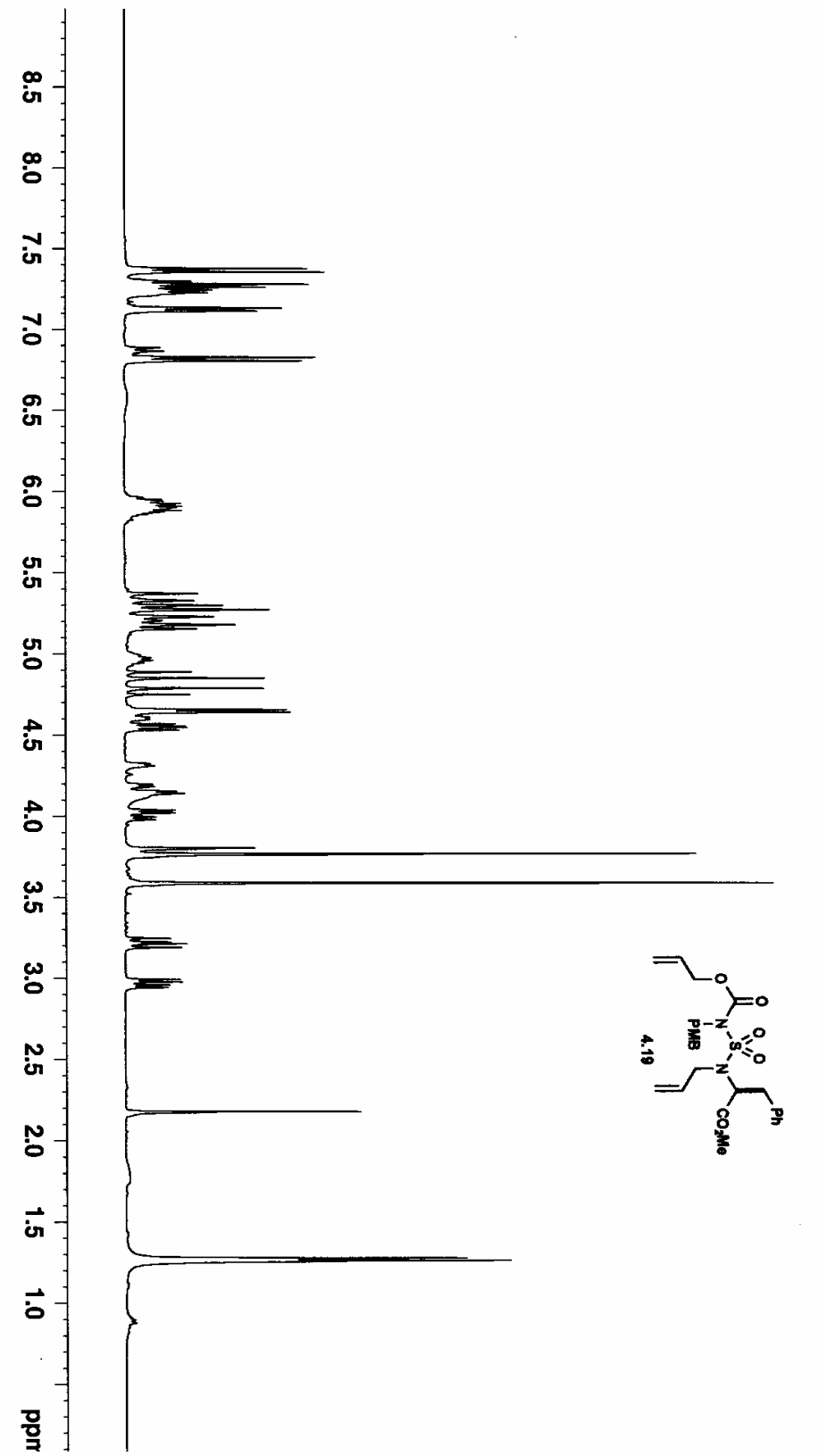
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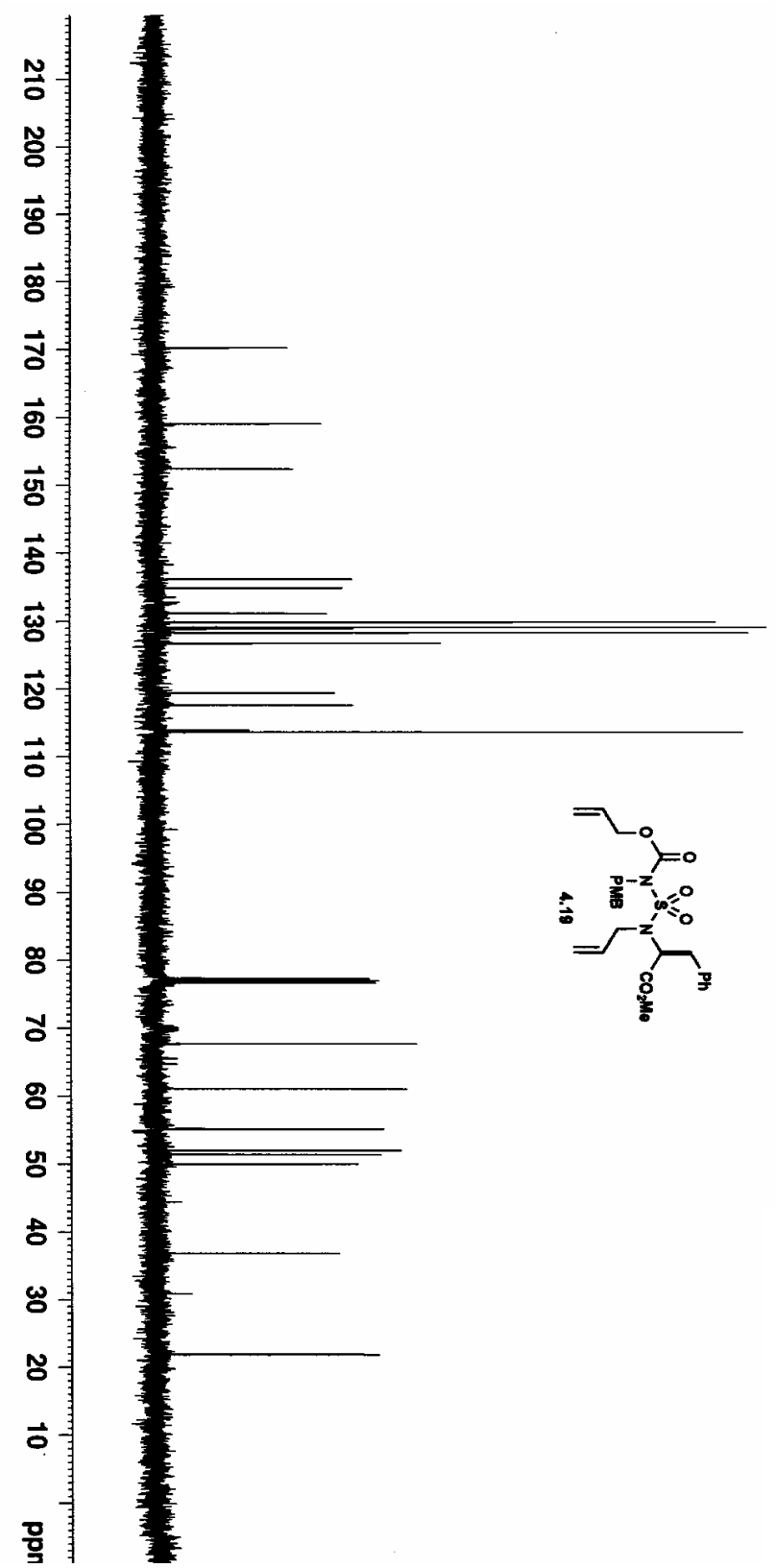
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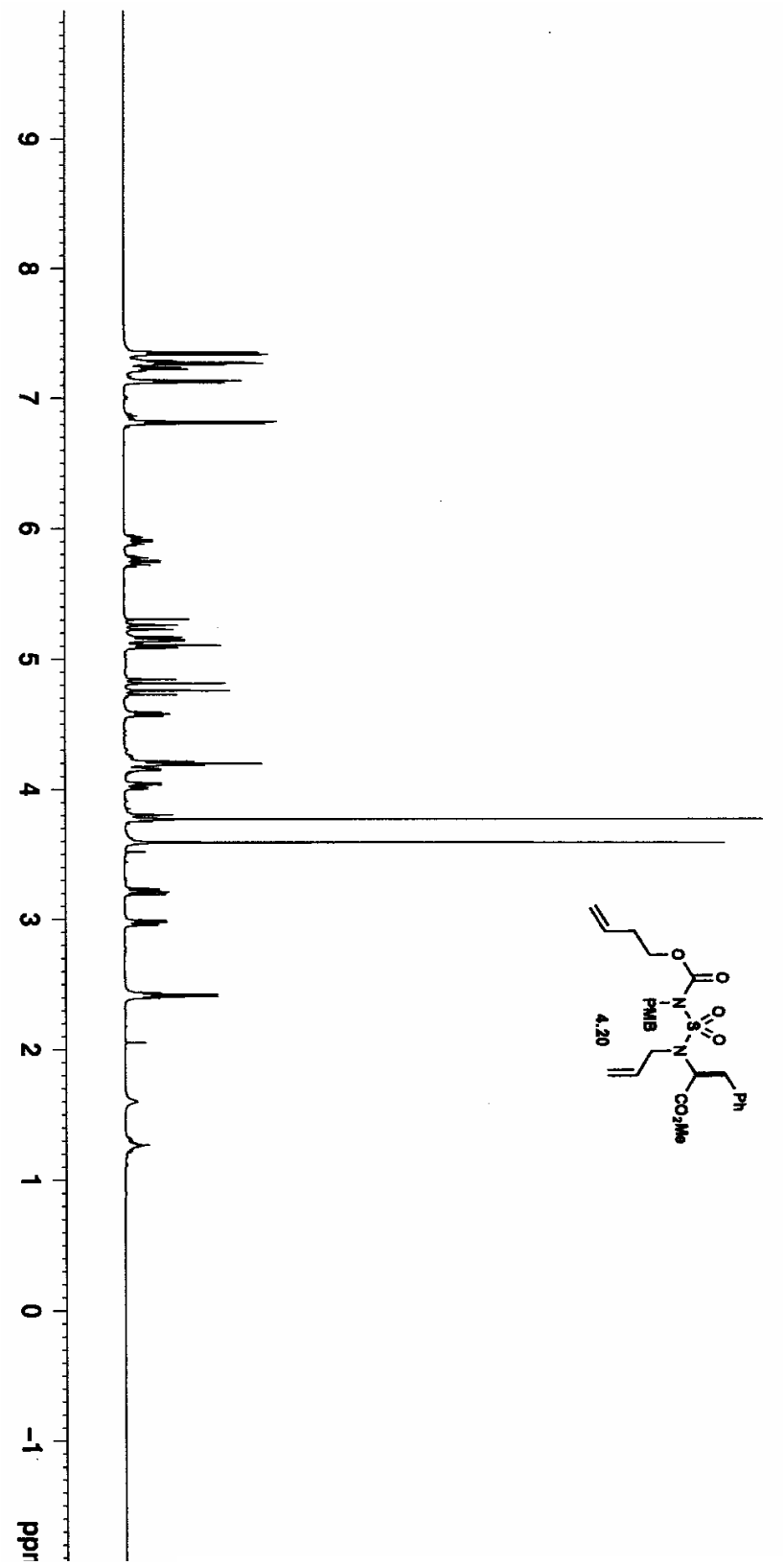
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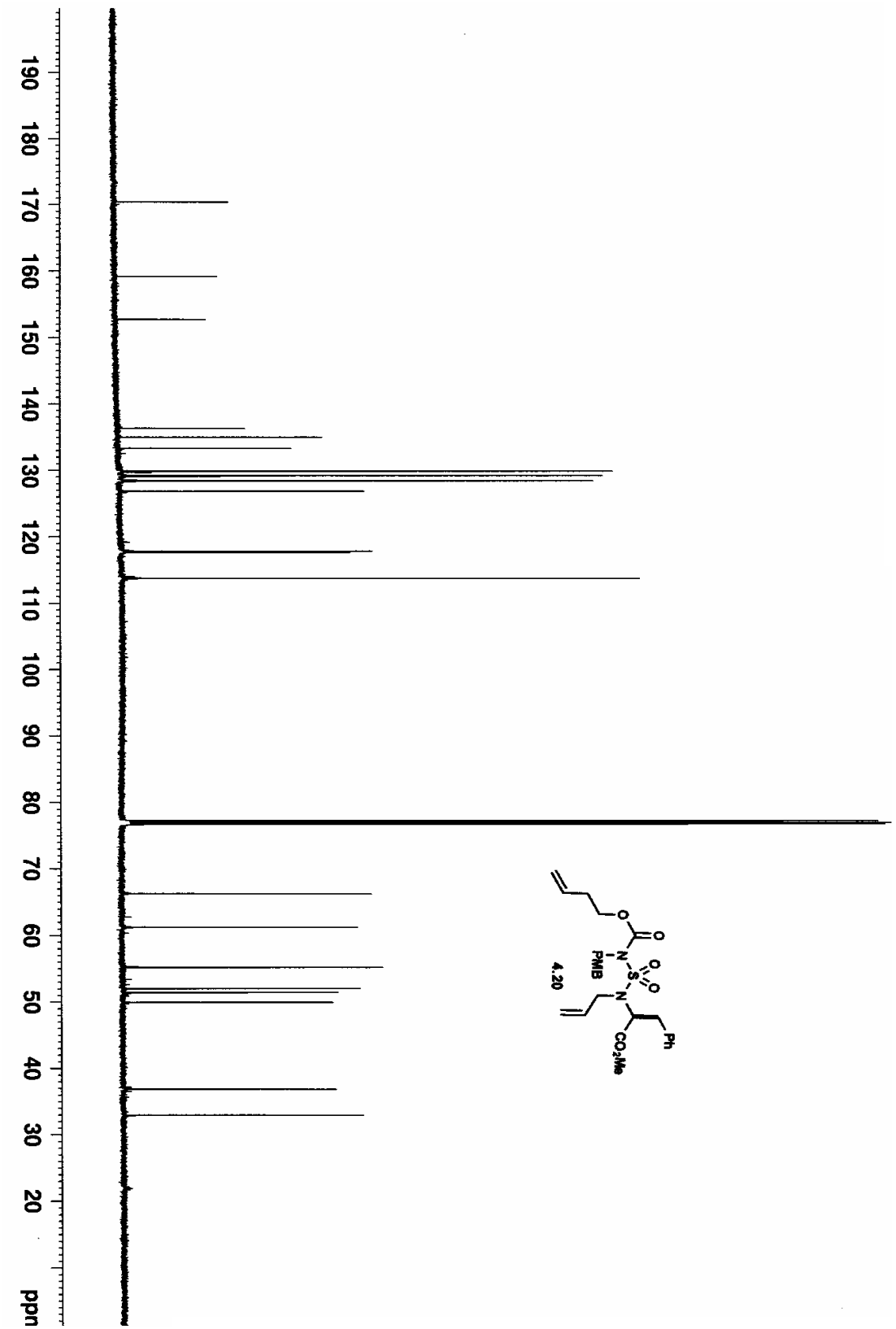
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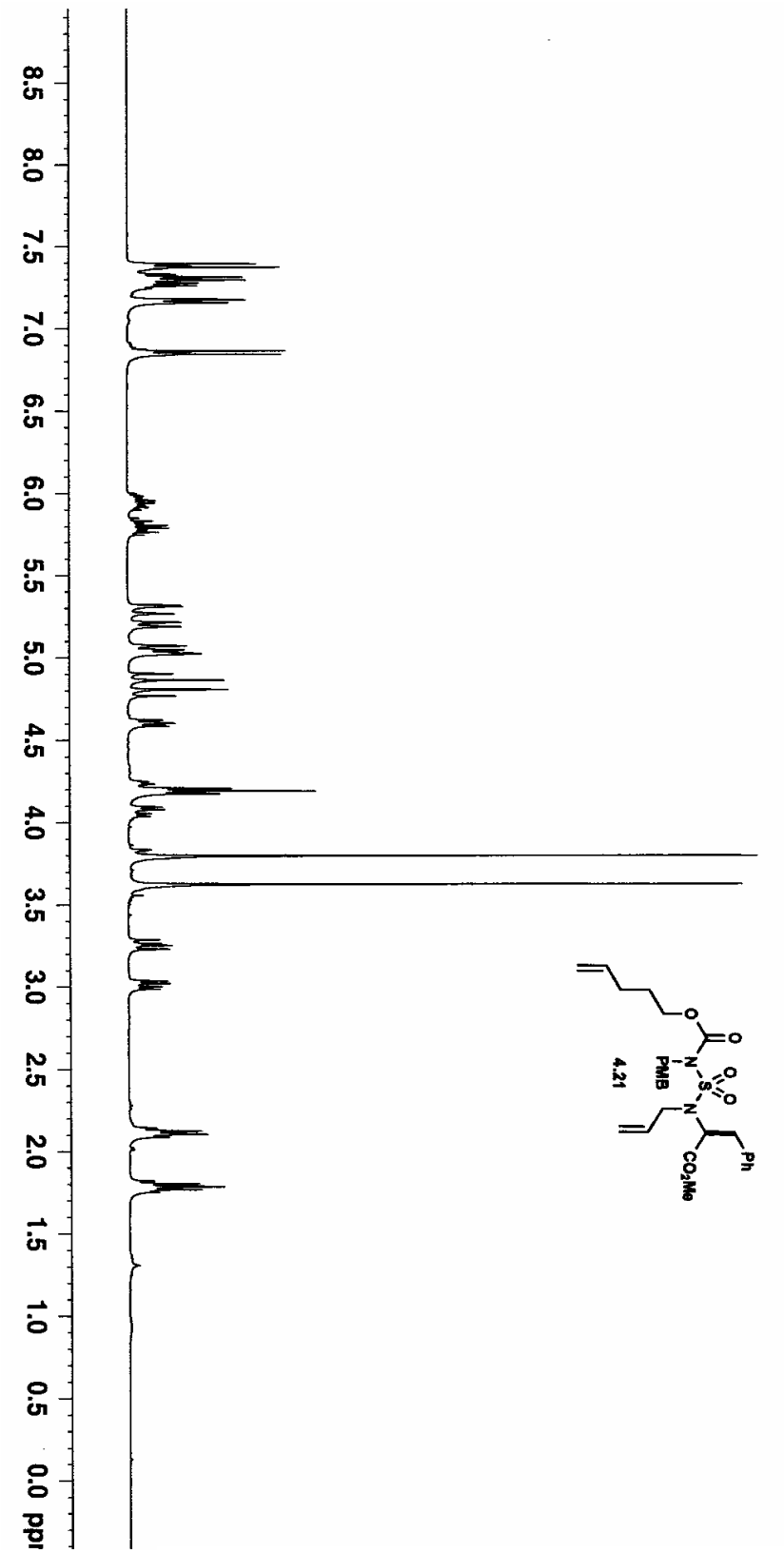
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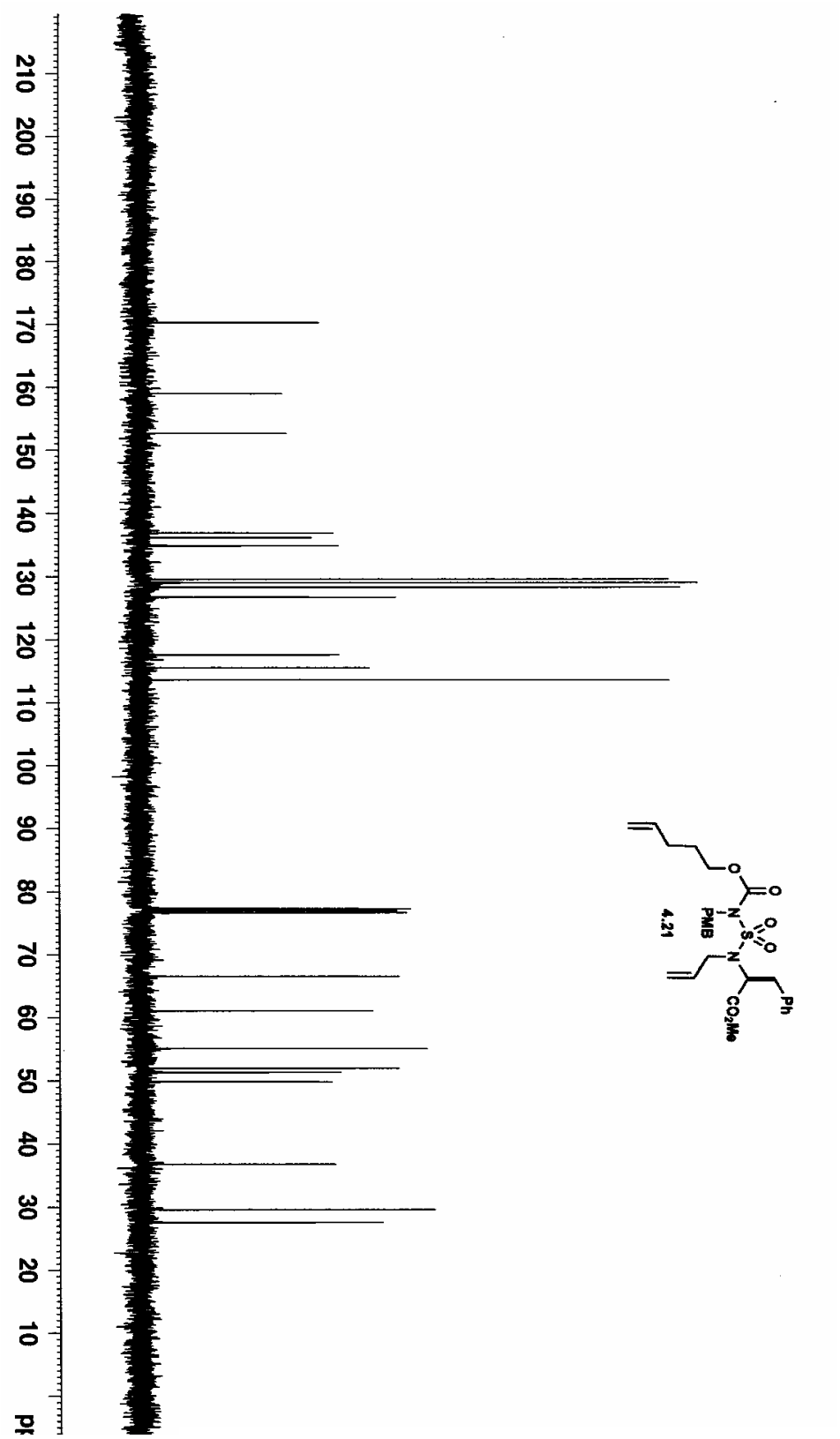
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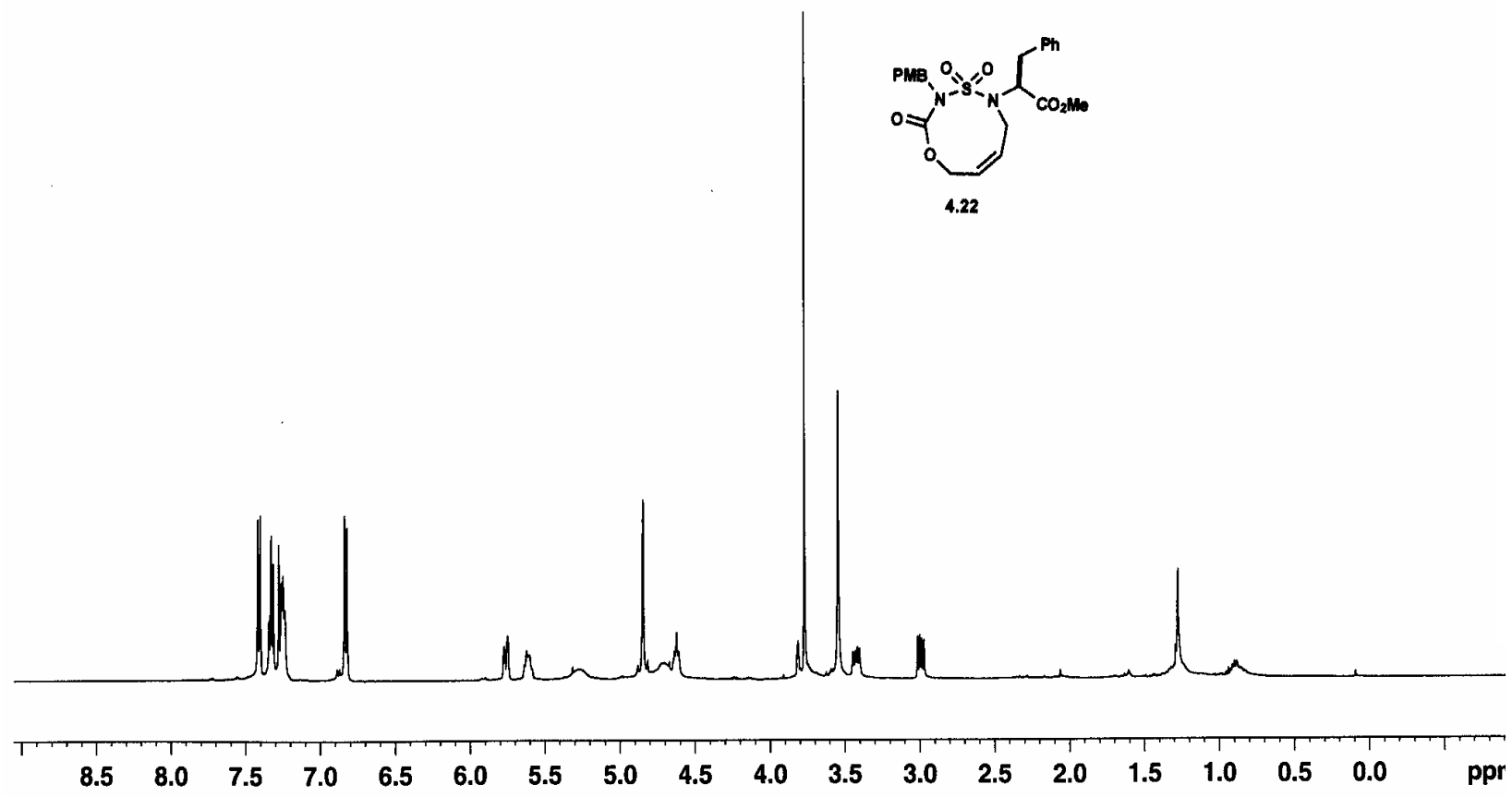
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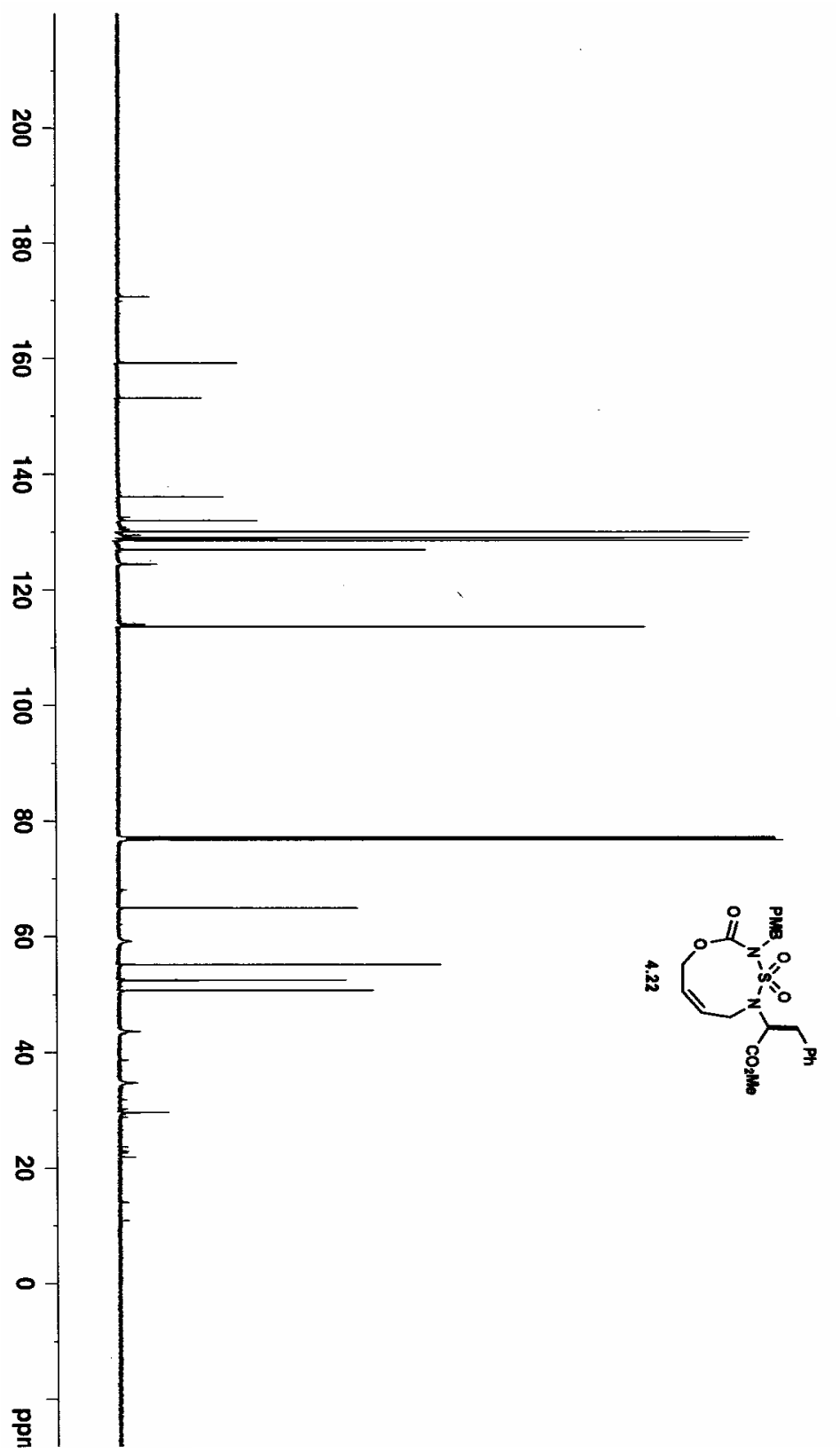
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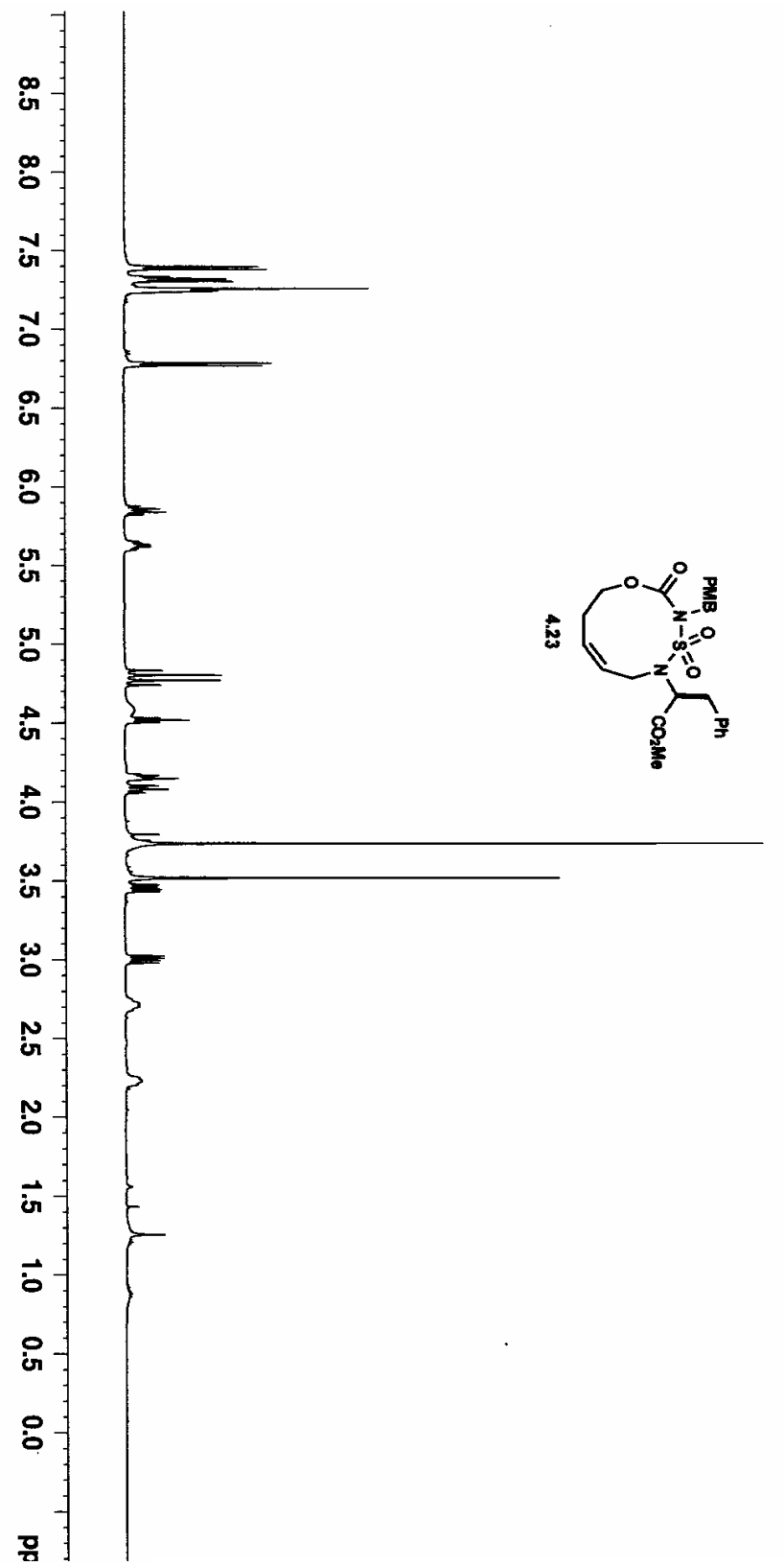
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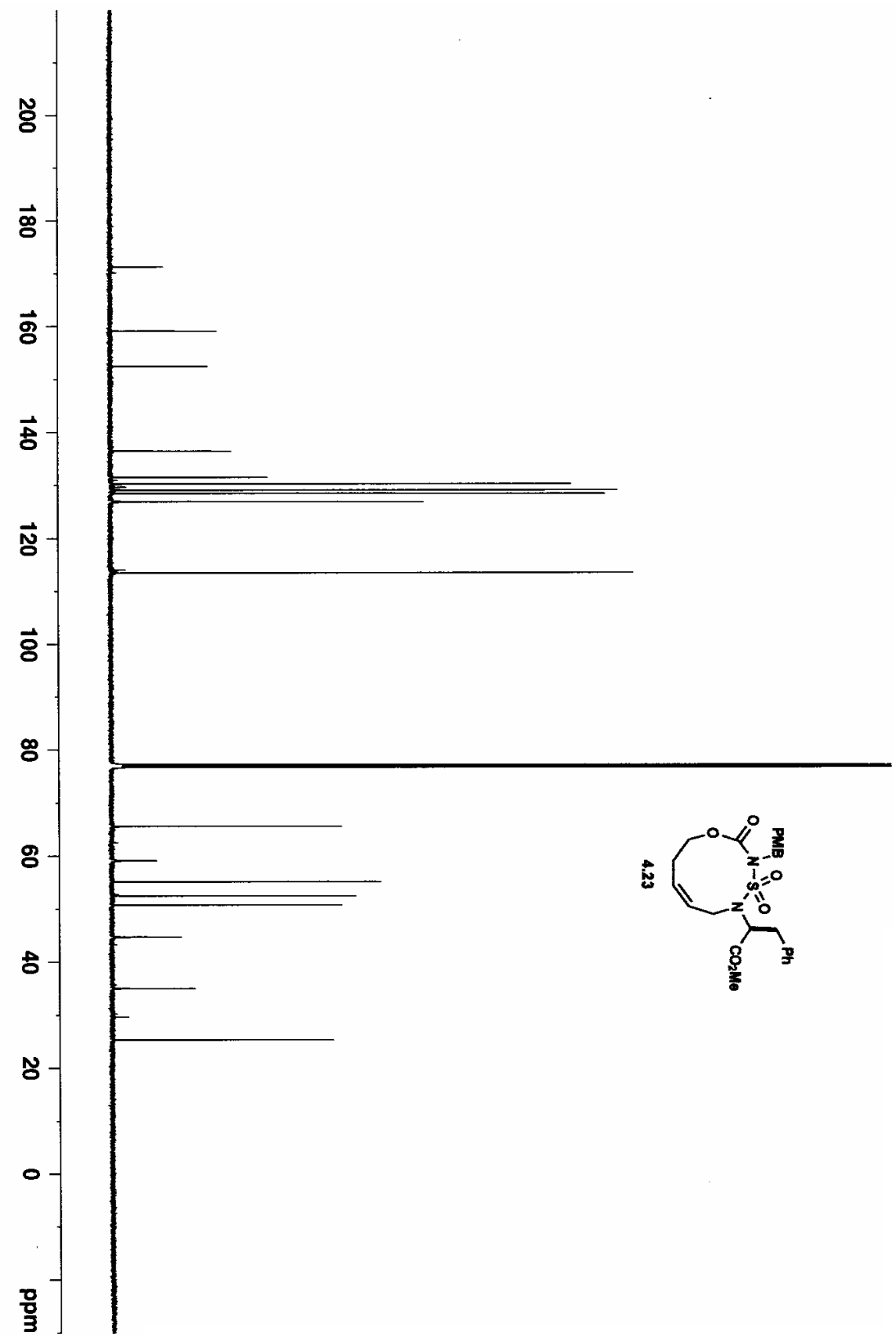
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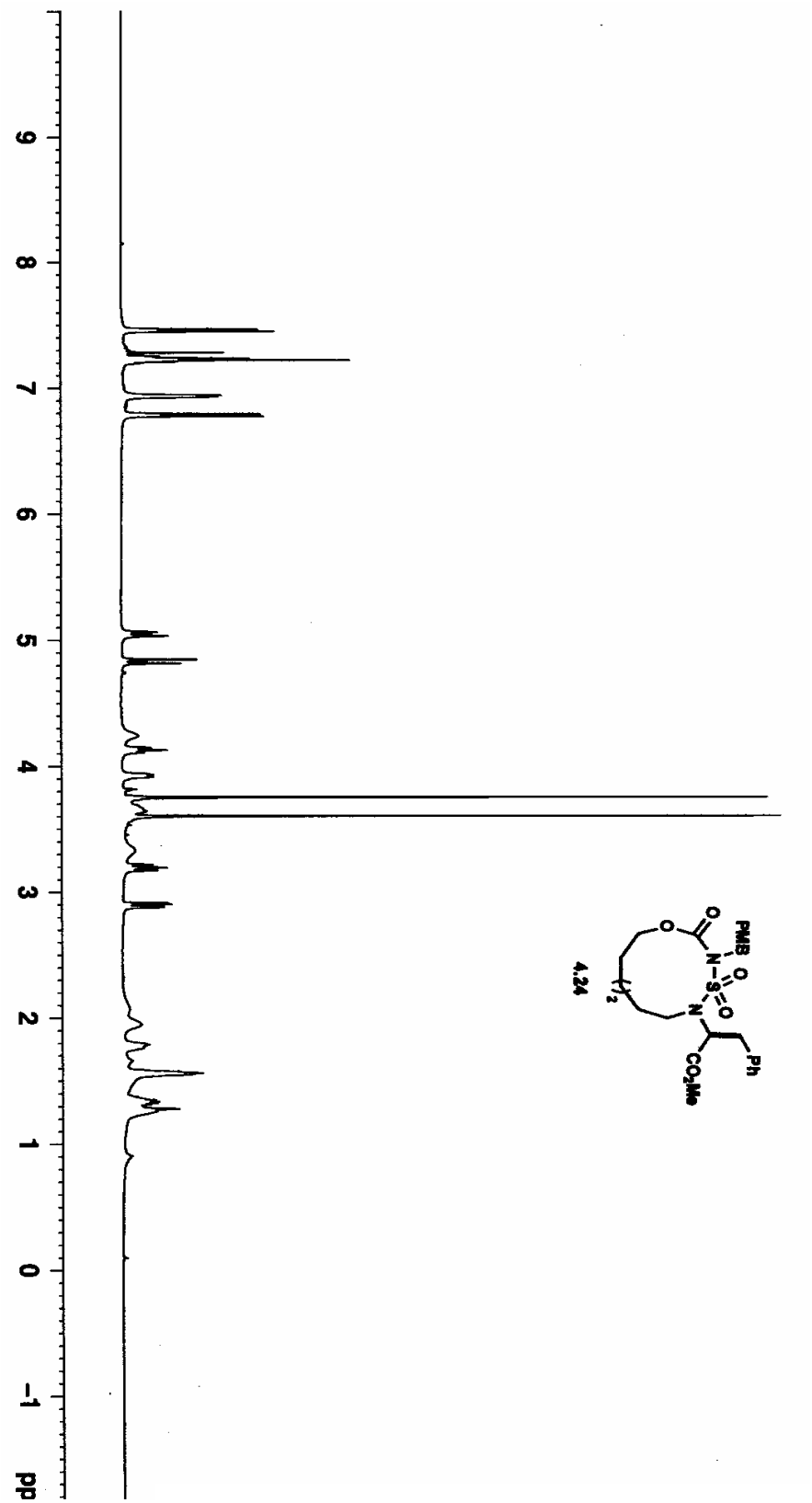
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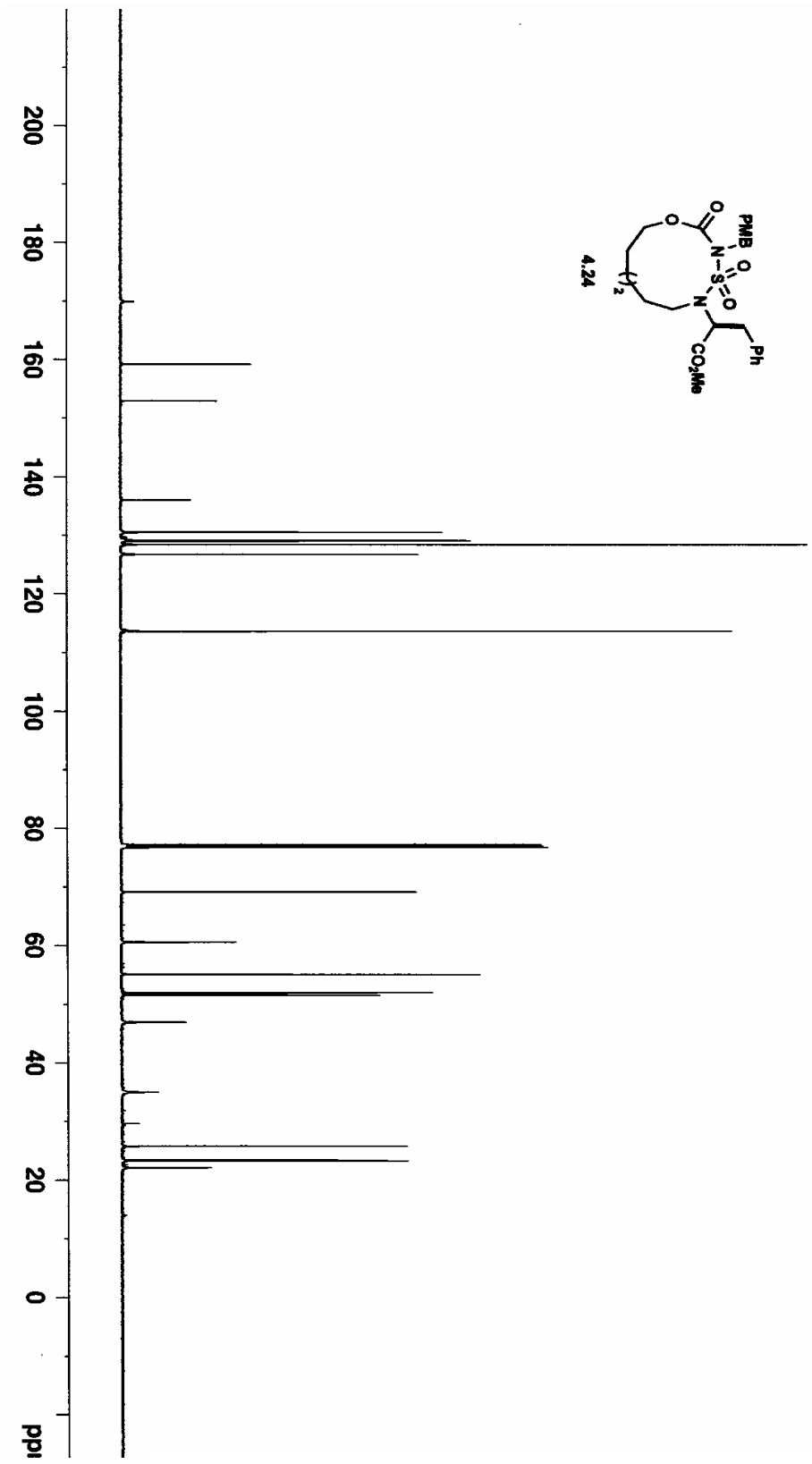
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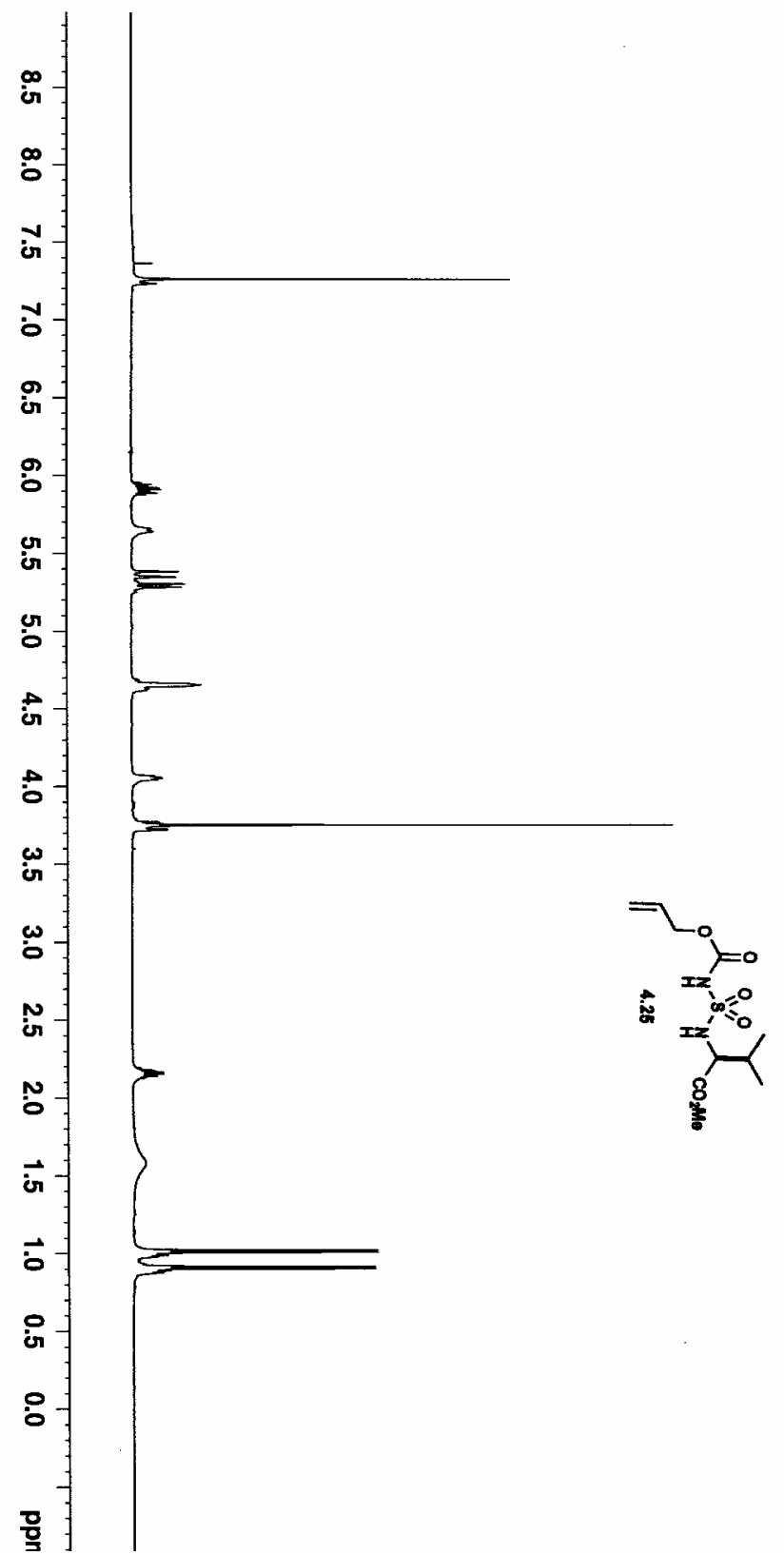
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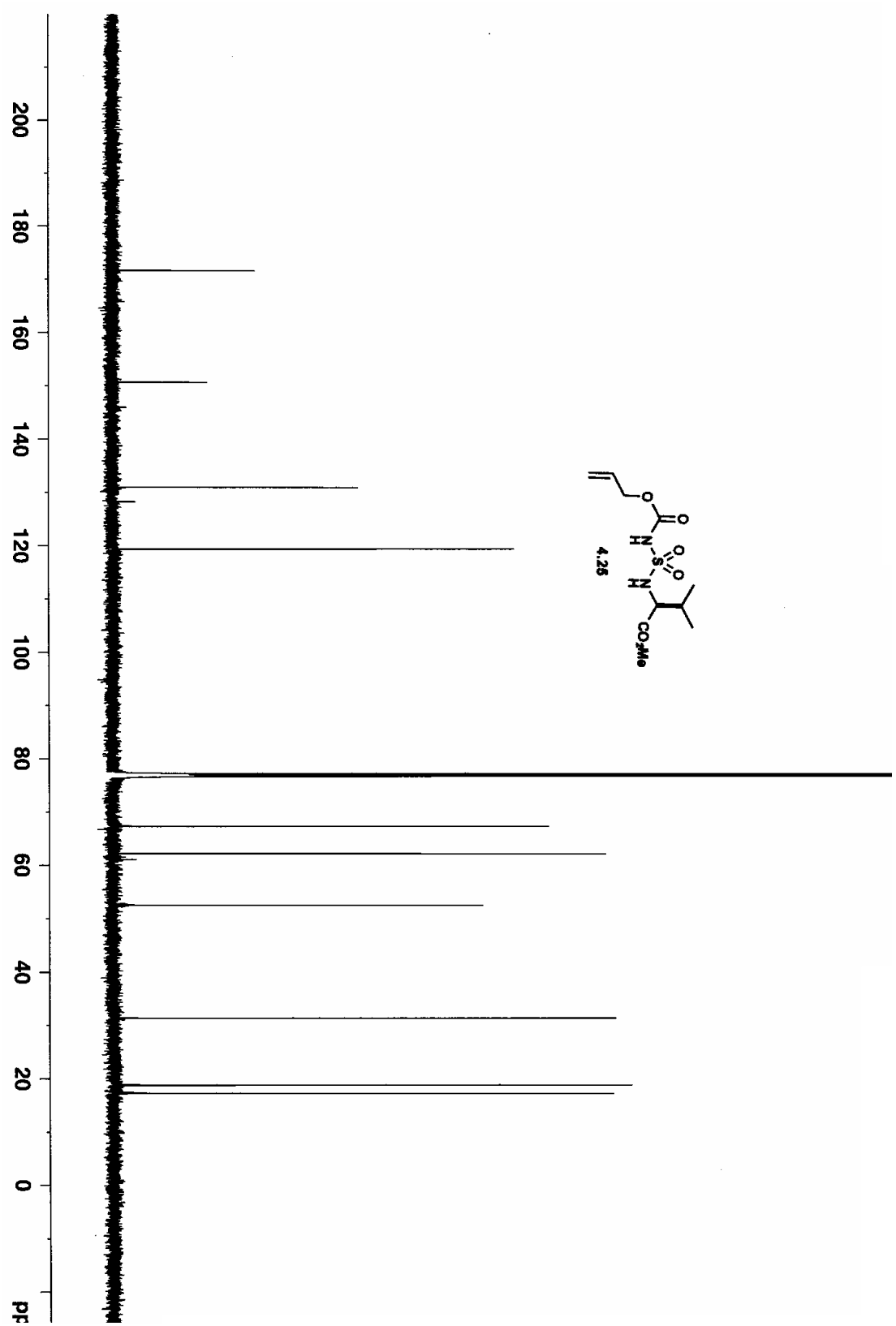
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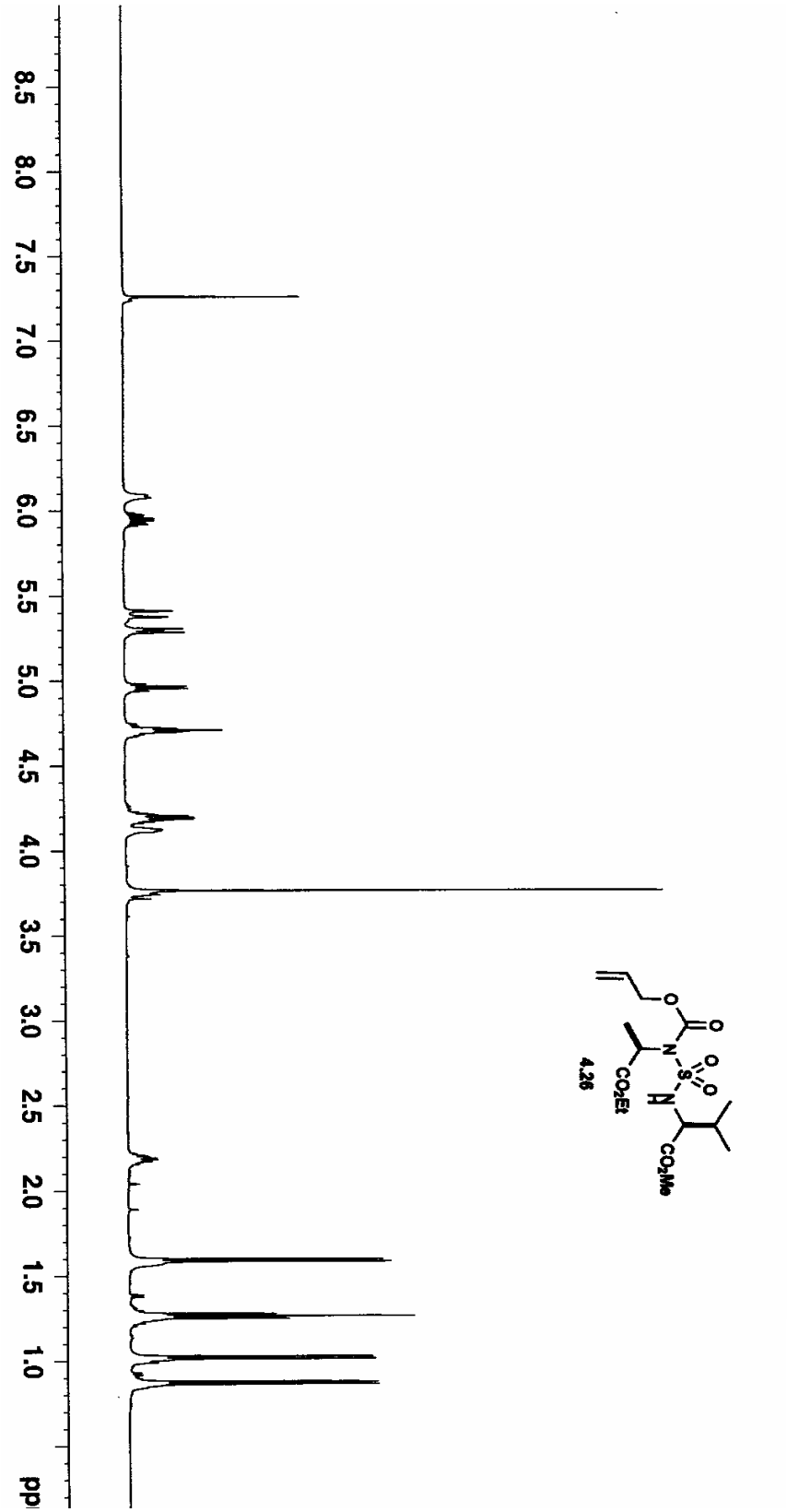
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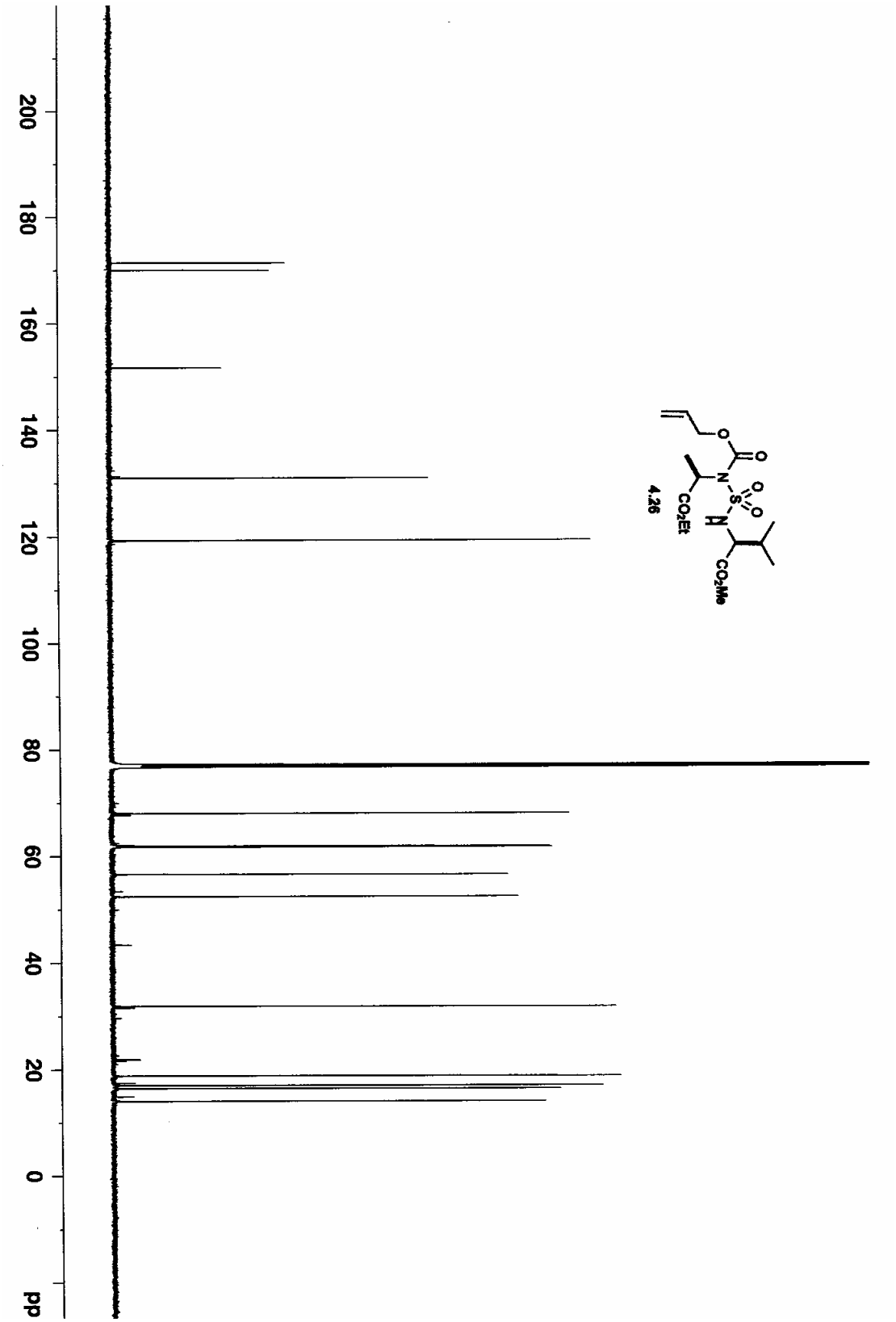
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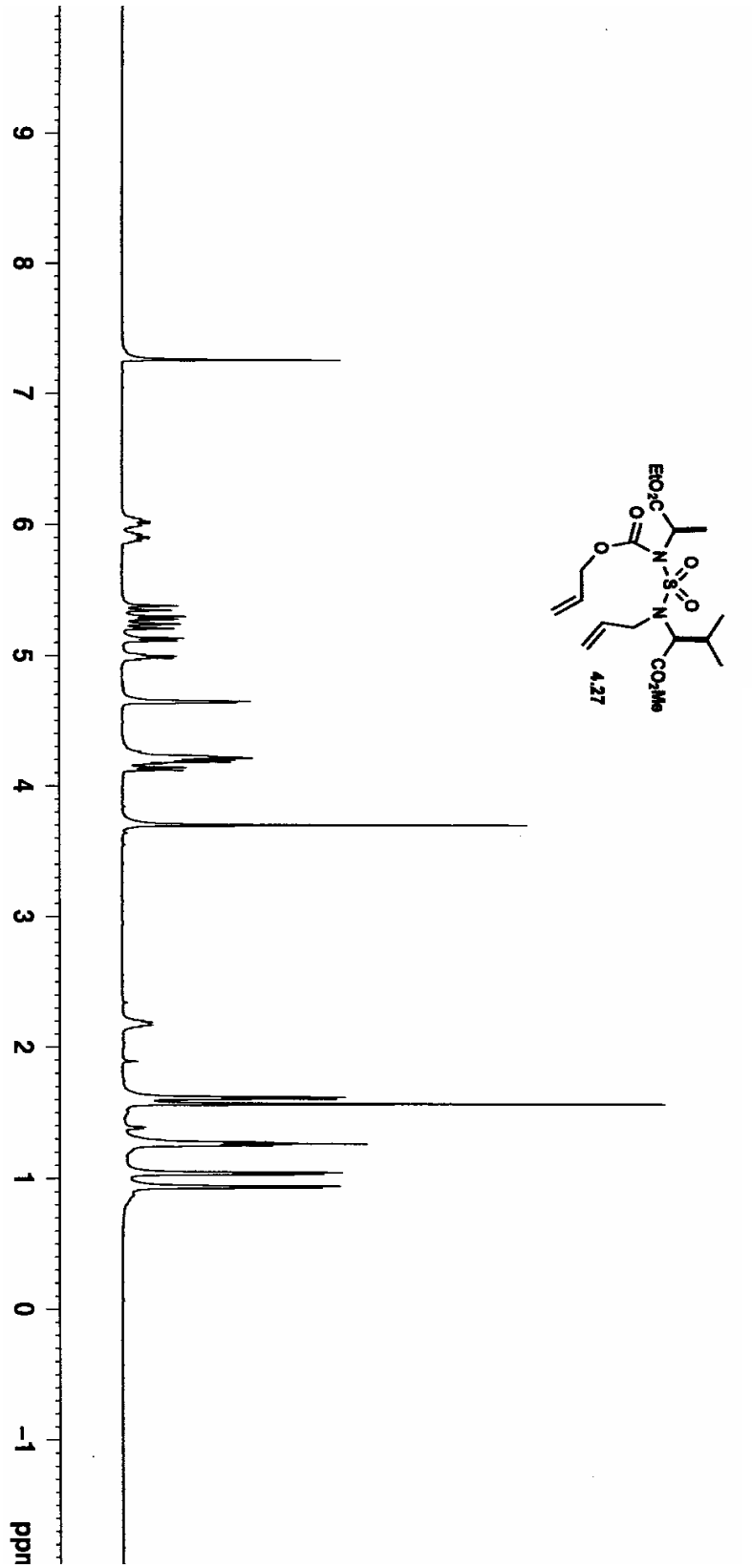
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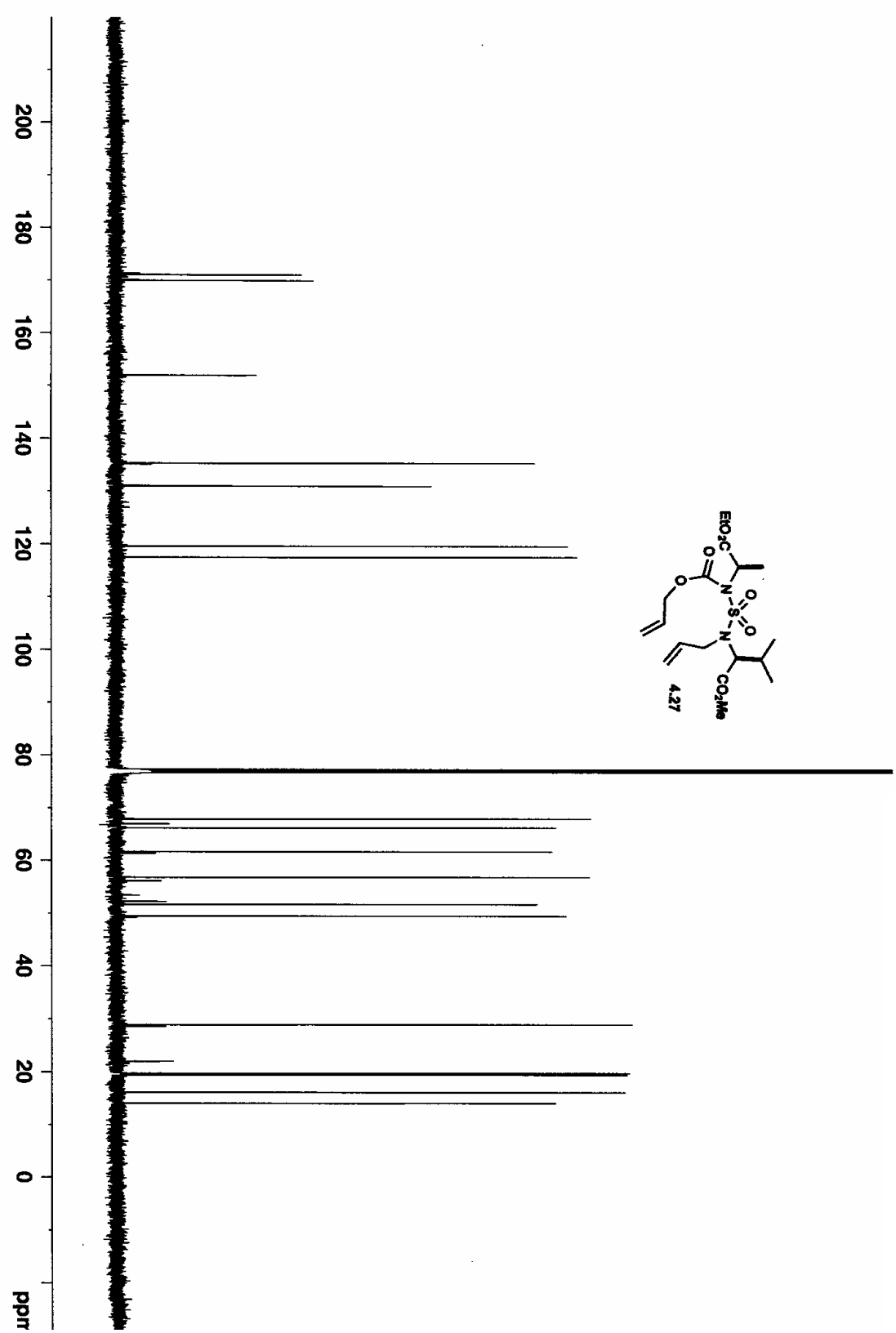
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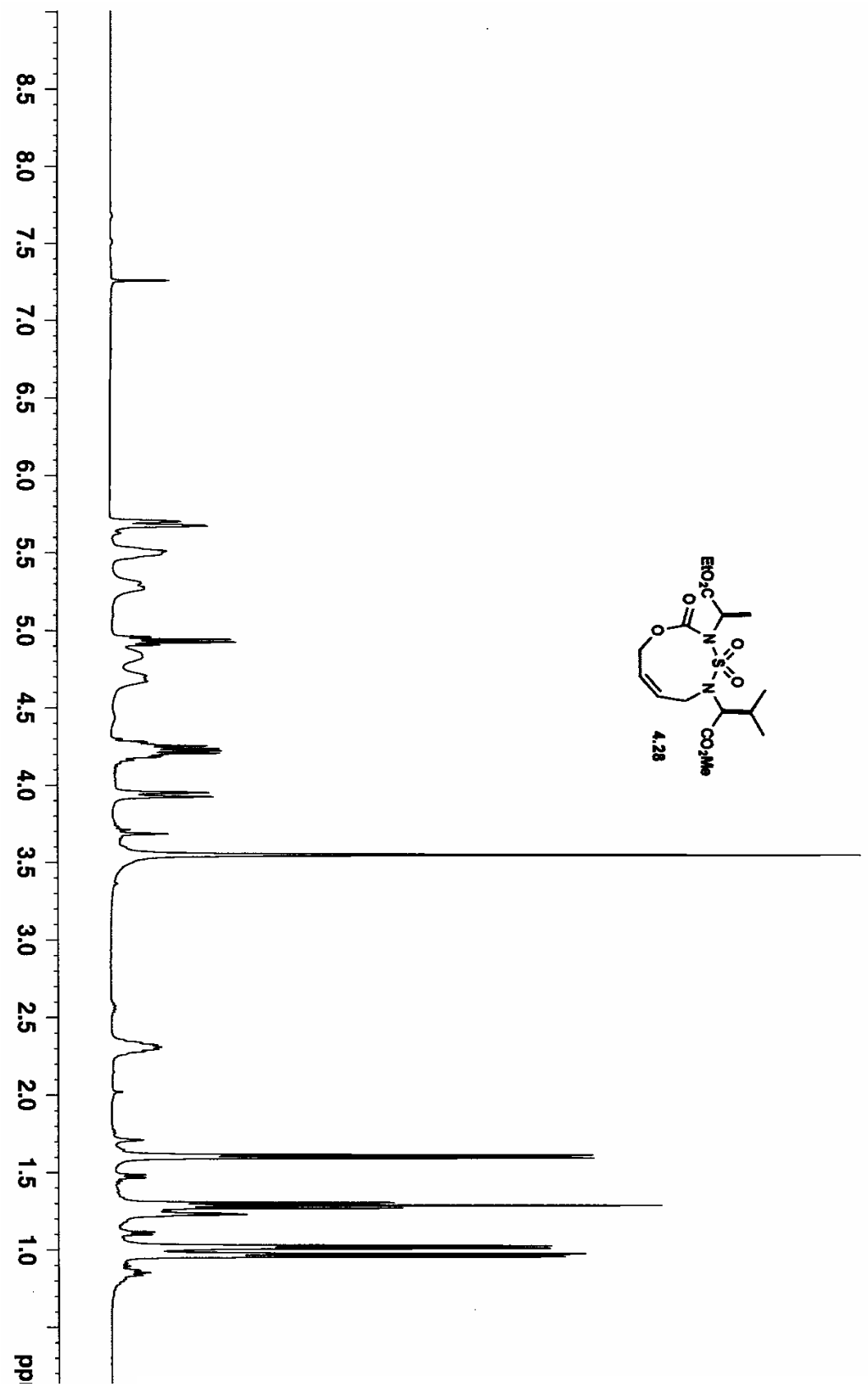
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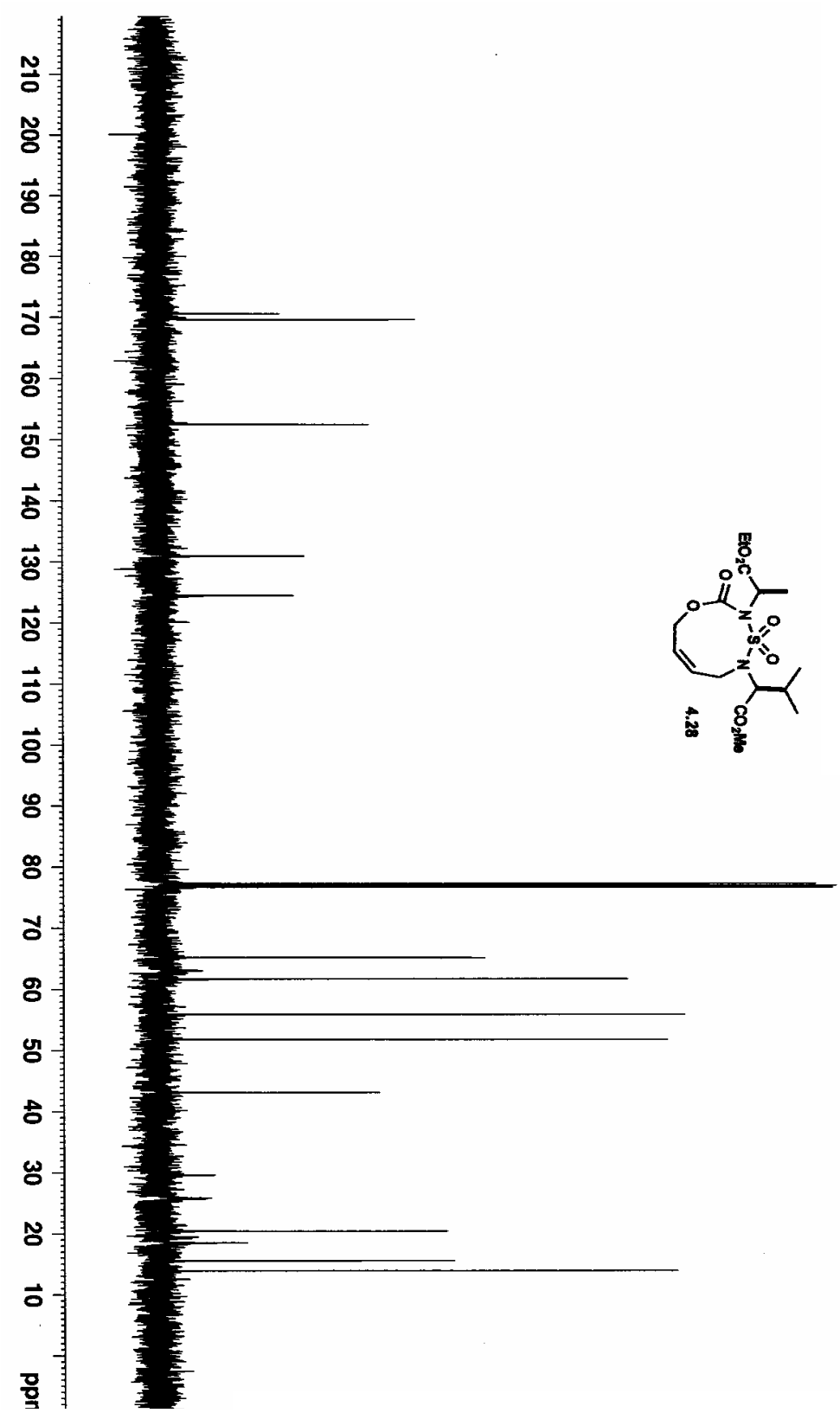
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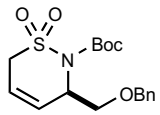
Crystal Structure Report

for

$C_{17}H_{23}NO_5S$




**2.6**

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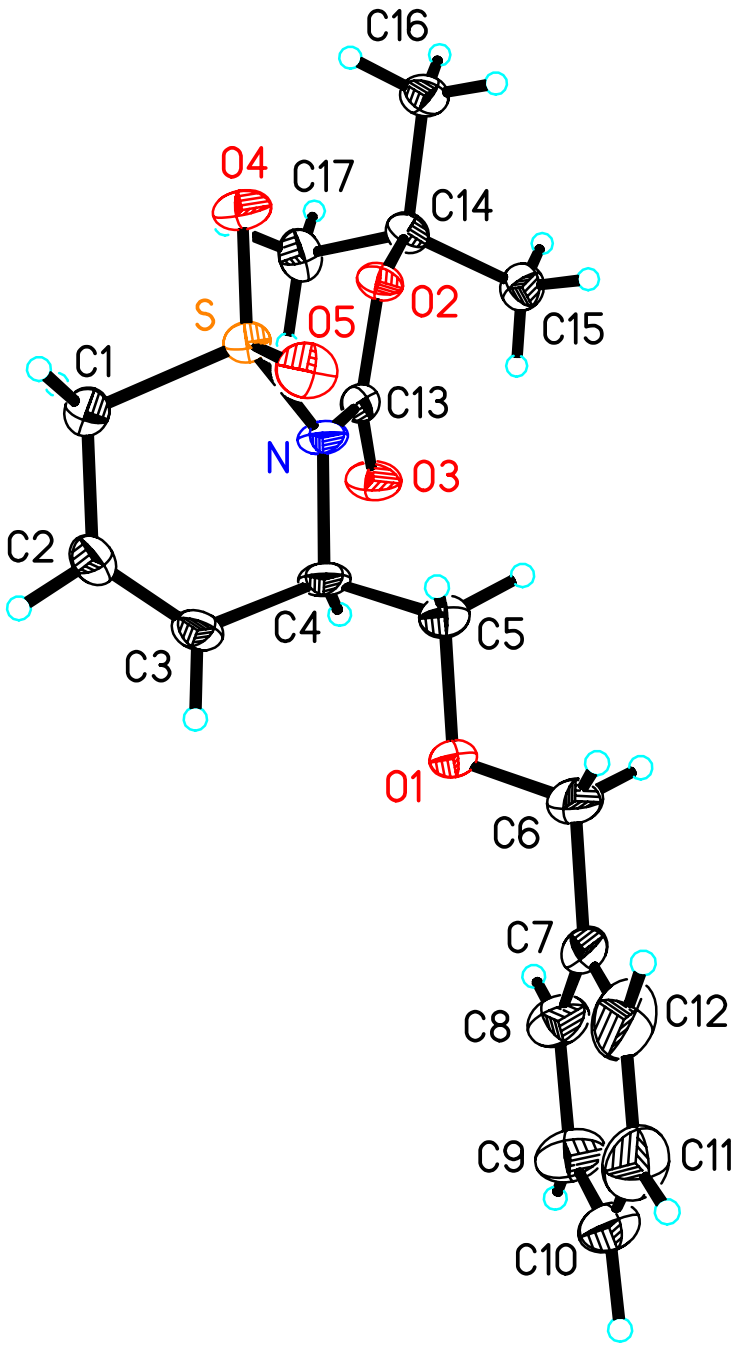
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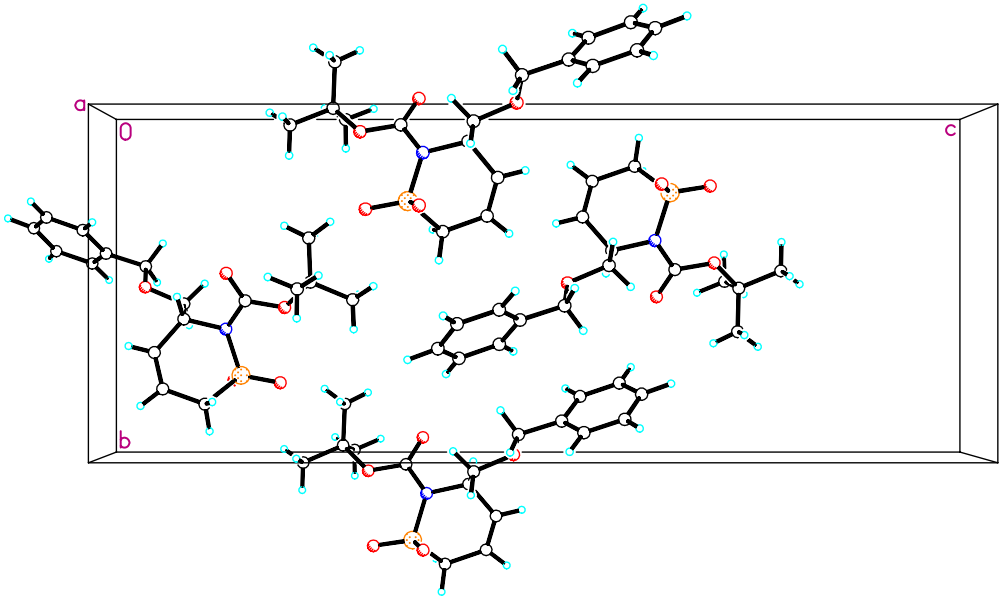
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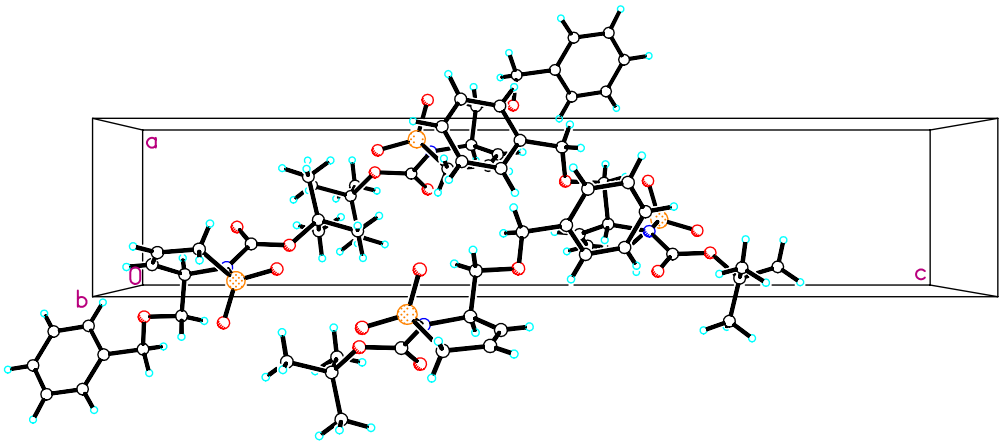
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**Comments**

The asymmetric unit contains one $C_{17}H_{23}NO_5S$ molecule (**2.6**). The oxygen atom for the ether linkage between C(5) and C(6) has two preferred orientations [O(1) and O(1')] in the crystal. This disorder produces two preferred orientations for the methylene hydrogens adjacent to this oxygen atom. The major orientation [represented by atom labels without a prime(')] for the disordered atoms is occupied 86% of the time and the minor orientation [represented by atom labels with a prime(')] is occupied 14% of the time. The major orientation is represented in the molecular plots by filled bonds and the minor orientation is represented by hollow bonds. All displacement ellipsoids are drawn at the 50% probability level.

**Brief Experimental Description to be Included as Text or as a Footnote at Time of Publication**

Colorless crystals of $C_{17}H_{23}NO_5S$ are, at 100(2) K, orthorhombic, space group $P2_12_12_1 - D_2^4$ (No. 19) (1) with **a** = 5.6080(4) Å, **b** = 11.232(1) Å, **c** = 28.414(2) Å, V = 1789.8(2) $Å^3$ and Z = 4 molecules {$d_{calcd}$ = 1.312 g/$cm^3$; $\mu_a$(MoK$\alpha$) = 0.206 $mm^{-1}$}. A full hemisphere of diffracted intensities (1850 10-second frames with a $\omega$ scan width of 0.30°) was measured for a single-domain specimen using graphite-monochromated MoK$\alpha$ radiation ($\lambda$= 0.71073 Å) on a Bruker SMART APEX CCD Single Crystal Diffraction System (2). X-rays were provided by a fine-focus sealed x-ray tube operated at 50kV and 30mA. Lattice constants were determined with the Bruker SAINT software package using peak centers for 7484 reflections. A total of 21992 integrated reflection intensities having 2$\theta$((MoK$\alpha$)< 61.07° were produced

using the Bruker program SAINT(3); 5427 of these were unique and gave $R_{int}$ = 0.041 with a coverage which was 99.7% complete. The data were corrected empirically for variable absorption effects using equivalent reflections; the relative transmission factors ranged from 0.934 to 1.000. The Bruker software package SHELXTL was used to solve the structure using "direct methods" techniques. All stages of weighted full-matrix least-squares refinement were conducted using $F_o^2$ data with the SHELXTL Version 6.10 software package(4).

The oxygen atom for the ether linkage between C(5) and C(6) has two preferred orientations [O(1) and O(1')] in the crystal. This disorder produces two preferred orientations for the methylene hydrogens adjacent to this oxygen atom. The major orientation [represented by atom labels without a prime(')] for the disordered atoms is occupied 86% of the time and the minor orientation [represented by atom labels with a prime(')] is occupied 14% of the time. All ordered hydrogen atoms were located in a difference Fourier and included in the structural model as independent isotropic atoms whose parameters were allowed to vary in least-squares refinement cycles. The eight disordered methylene hydrogen atoms were included into the structural model as idealized atoms (assuming $sp^3$-hybridization of the carbon atoms and a C-H bond length of 0.99 Å).

The final structural model incorporated anisotropic thermal parameters for all nonhydrogen atoms except the minor-occupancy disordered ether oxygen atom O(1'). Isotropic thermal parameters were incorporated for this oxygen atom and all hydrogen atoms. The isotropic thermal parameters of all eight idealized hydrogen

atoms were fixed at values 1.2 times the equivalent isotropic thermal parameter of the carbon atom to which they are covalently bonded. A total of 298 parameters were refined using no restraints, 5427 data and weights of $w = 1/ [\sigma^2(F^2) + (0.0595\ P)^2]$, where $P = [F_o^2 + 2F_c^2] / 3$. Final agreement factors at convergence are: $R_1$(unweighted, based on F) = 0.040 for 4885 independent absorption-corrected "observed" reflections having $2\theta(MoK\alpha) < 61.07°$ and $I > 2\sigma(I)$; $R_1$(unweighted, based on F) = 0.044 and $wR_2$(weighted, based on $F^2$) = 0.095 for all 5427 independent absorption-corrected reflections having $2\theta(MoK\alpha) < 61.07°$. The largest shift/s.u. was 0.001 in the final refinement cycle. The final difference map had maxima and minima of 0.52 and -0.35 $e^-/Å^3$, respectively. The absolute configuration was determined experimentally using anomalous dispersion of the x-rays; the "Flack" absolute structure parameter refined to a final value of 0.02(5).

**Acknowledgment**

The authors thank the National Science Foundation (grant CHE-0079282) and the University of Kansas for funds to purchase the x-ray instrument and computers.

**References**

(1) International Tables for Crystallography, Vol A, 4th ed., Kluwer: Boston (1996).
(2) Data Collection: SMART Software Reference Manual (1998). Bruker-AXS, 5465 E. Cheryl Parkway, Madison, WI 53711-5373 USA.
(3) Data Reduction: SAINT Software Reference Manual (1998). Bruker-AXS, 6300 Enterprise Dr., Madison, WI 53719-1173, USA.
(4) G. M. Sheldrick (2000). SHELXTL Version 6.10 Reference Manual. Bruker-AXS, 5465 E. Cheryl Parkway, Madison, WI 53711-5373 USA.

**Table A1**. Crystal data and structure refinement for $C_{17}H_{23}NO_5S$.

| | | |
|---|---|---|
| Empirical formula | $C_{17}H_{23}NO_5S$ | |
| Formula weight | 353.42 | |
| Temperature | 100(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | $P2_12_12_1 - D_2^4$ (No. 19) | |
| Unit cell dimensions | **a** = 5.6080(4) Å | **α** = 90.000° |
| | **b** = 11.232(1) Å | **β** = 90.000° |
| | **c** = 28.414(2) Å | **γ** = 90.000° |
| Volume | 1789.8(2) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.312 $Mg/m^3$ | |
| Absorption coefficient | 0.206 $mm^{-1}$ | |
| F(000) | 752 | |
| Crystal size | 0.38 x 0.28 x 0.16 $mm^3$ | |
| Theta range for data collection | 2.31° to 30.54° | |
| Index ranges | $-8 \le h \le 7$, $-15 \le k \le 16$, $-40 \le l \le 40$ | |
| Reflections collected | 21992 | |
| Independent reflections | 5427 [$R_{int}$ = 0.041] | |
| Completeness to theta = 30.54° | 99.7 % | |
| Absorption correction | Empirical | |
| Max. and min. transmission | 1.000 and 0.934 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 5427 / 0 / 298 | |
| Goodness-of-fit on $F^2$ | 0.982 | |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.040, $wR_2$ = 0.093 | |
| R indices (all data) | $R_1$ = 0.044, $wR_2$ = 0.095 | |
| Absolute structure parameter | 0.02(5) | |
| Largest diff. peak and hole | 0.52 and -0.35 $e^-/Å^3$ | |

---

$R_1 = \Sigma \, ||F_o| - |F_c|| \, / \, \Sigma \, |F_o|$

$wR_2 = \{ \, \Sigma \, [w(F_o^2 - F_c^2)^2] \, / \, \Sigma \, [w(F_o^2)^2] \, \}^{1/2}$

**Table A2**. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$ x $10^3$) for $C_{17}H_{23}NO_5S$. U(eq) is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| S | 755(1) | 7685(1) | 1492(1) | 19(1) |
| O(1) | -1583(3) | 5033(1) | 297(1) | 27(1) |
| O(1') | -2767(15) | 5442(7) | 340(2) | 14(2) |
| O(2) | 2750(2) | 5658(1) | 2040(1) | 20(1) |
| O(3) | 3822(2) | 4661(1) | 1384(1) | 28(1) |
| O(4) | 1449(2) | 7896(1) | 1967(1) | 27(1) |
| O(5) | -1671(2) | 7865(1) | 1357(1) | 31(1) |
| N | 1456(3) | 6301(1) | 1329(1) | 22(1) |
| C(1) | 2611(3) | 8510(1) | 1110(1) | 24(1) |
| C(2) | 2403(3) | 8065(1) | 614(1) | 27(1) |
| C(3) | 1661(3) | 6997(1) | 496(1) | 26(1) |
| C(4) | 1017(3) | 6003(1) | 825(1) | 27(1) |
| C(5) | -1487(4) | 5539(2) | 765(1) | 44(1) |
| C(6) | -3613(6) | 4381(3) | 247(1) | 89(1) |
| C(7) | -3993(4) | 3979(2) | -249(1) | 38(1) |
| C(8) | -2303(4) | 3287(2) | -476(1) | 36(1) |
| C(9) | -2692(4) | 2889(2) | -928(1) | 40(1) |
| C(10) | -4759(4) | 3179(2) | -1158(1) | 42(1) |
| C(11) | -6433(4) | 3871(2) | -944(1) | 49(1) |
| C(12) | -6056(4) | 4264(2) | -485(1) | 53(1) |
| C(13) | 2824(3) | 5462(1) | 1583(1) | 19(1) |
| C(14) | 4261(3) | 4922(1) | 2361(1) | 21(1) |
| C(15) | 3556(3) | 3624(2) | 2331(1) | 27(1) |
| C(16) | 3594(4) | 5433(2) | 2838(1) | 27(1) |
| C(17) | 6861(3) | 5139(2) | 2248(1) | 29(1) |

**Table A3**. Bond lengths [Å] for $C_{17}H_{23}NO_5S$.

| | | | |
|---|---|---|---|
| S-O(4) | 1.423(1) | C(6)-H(6B) | 0.99 |
| S-O(5) | 1.428(1) | C(7)-C(12) | 1.375(3) |
| S-N | 1.669(1) | C(7)-C(8) | 1.384(3) |
| S-C(1) | 1.766(2) | C(8)-C(9) | 1.380(3) |
| O(1)-C(6) | 1.361(3) | C(8)-H(8) | 0.95(2) |
| O(1)-C(5) | 1.448(2) | C(9)-C(10) | 1.370(3) |
| O(2)-C(13) | 1.318(2) | C(9)-H(9) | 0.90(3) |
| O(2)-C(14) | 1.495(2) | C(10)-C(11) | 1.362(3) |
| O(3)-C(13) | 1.201(2) | C(10)-H(10) | 1.02(2) |
| N-C(13) | 1.414(2) | C(11)-C(12) | 1.392(3) |
| N-C(4) | 1.490(2) | C(11)-H(11) | 0.98(3) |
| C(1)-C(2) | 1.499(2) | C(12)-H(12) | 1.00(3) |
| C(1)-H(1A) | 0.98(2) | C(14)-C(15) | 1.513(2) |
| C(1)-H(1B) | 0.89(2) | C(14)-C(17) | 1.513(2) |
| C(2)-C(3) | 1.313(2) | C(14)-C(16) | 1.521(2) |
| C(2)-H(2) | 0.92(2) | C(15)-H(15A) | 0.90(2) |
| C(3)-C(4) | 1.500(2) | C(15)-H(15B) | 0.95(2) |
| C(3)-H(3) | 0.90(2) | C(15)-H(15C) | 1.02(2) |
| C(4)-C(5) | 1.507(3) | C(16)-H(16A) | 0.99(2) |
| C(4)-H(4) | 0.93(2) | C(16)-H(16B) | 0.95(2) |
| C(5)-H(5A) | 0.99 | C(16)-H(16C) | 0.97(2) |
| C(5)-H(5B) | 0.99 | C(17)-H(17A) | 1.03(2) |
| C(6)-C(7) | 1.495(3) | C(17)-H(17B) | 1.00(2) |
| C(6)-H(6A) | 0.99 | C(17)-H(17C) | 0.96(2) |

**Table A4**. Bond angles [°] for $C_{17}H_{23}NO_5S$.

| | | | |
|---|---|---|---|
| O(4)-S-O(5) | 119.45(7) | O(1)-C(5)-H(5B) | 110.5 |
| O(4)-S-N | 110.72(6) | C(4)-C(5)-H(5B) | 110.5 |
| O(5)-S-N | 106.32(7) | H(5A)-C(5)-H(5B) | 108.7 |
| O(4)-S-C(1) | 109.52(8) | O(1)-C(6)-C(7) | 112.33(17) |
| O(5)-S-C(1) | 108.83(8) | O(1)-C(6)-H(6A) | 109.1 |
| N-S-C(1) | 100.28(7) | C(7)-C(6)-H(6A) | 109.1 |
| C(6)-O(1)-C(5) | 109.75(16) | O(1)-C(6)-H(6B) | 109.1 |
| C(13)-O(2)-C(14) | 119.36(11) | C(7)-C(6)-H(6B) | 109.1 |
| C(13)-N-C(4) | 115.46(12) | H(6A)-C(6)-H(6B) | 107.9 |
| C(13)-N-S | 127.38(10) | C(12)-C(7)-C(8) | 118.69(16) |
| C(4)-N-S | 115.95(10) | C(12)-C(7)-C(6) | 120.6(2) |
| C(2)-C(1)-S | 110.93(11) | C(8)-C(7)-C(6) | 120.7(2) |
| C(2)-C(1)-H(1A) | 113.3(10) | C(9)-C(8)-C(7) | 120.47(19) |
| S-C(1)-H(1A) | 102.6(11) | C(9)-C(8)-H(8) | 119.9(14) |
| C(2)-C(1)-H(1B) | 112.7(13) | C(7)-C(8)-H(8) | 119.7(13) |
| S-C(1)-H(1B) | 104.7(13) | C(10)-C(9)-C(8) | 120.07(19) |
| H(1A)-C(1)-H(1B) | 111.9(18) | C(10)-C(9)-H(9) | 119.0(15) |
| C(3)-C(2)-C(1) | 124.67(14) | C(8)-C(9)-H(9) | 120.9(15) |
| C(3)-C(2)-H(2) | 115.3(14) | C(11)-C(10)-C(9) | 120.40(19) |
| C(1)-C(2)-H(2) | 120.0(14) | C(11)-C(10)-H(10) | 119.7(14) |
| C(2)-C(3)-C(4) | 126.64(14) | C(9)-C(10)-H(10) | 119.8(14) |
| C(2)-C(3)-H(3) | 119.8(12) | C(10)-C(11)-C(12) | 119.6(2) |
| C(4)-C(3)-H(3) | 113.5(12) | C(10)-C(11)-H(11) | 123.6(17) |
| N-C(4)-C(3) | 113.03(13) | C(12)-C(11)-H(11) | 116.7(17) |
| N-C(4)-C(5) | 109.95(14) | C(7)-C(12)-C(11) | 120.70(19) |
| C(3)-C(4)-C(5) | 114.25(15) | C(7)-C(12)-H(12) | 117.0(17) |
| N-C(4)-H(4) | 104.3(10) | C(11)-C(12)-H(12) | 122.3(17) |
| C(3)-C(4)-H(4) | 110.4(11) | O(3)-C(13)-O(2) | 127.20(13) |
| C(5)-C(4)-H(4) | 104.1(11) | O(3)-C(13)-N | 120.79(12) |
| O(1)-C(5)-C(4) | 105.96(16) | O(2)-C(13)-N | 111.96(12) |
| O(1)-C(5)-H(5A) | 110.5 | O(2)-C(14)-C(15) | 110.60(12) |
| C(4)-C(5)-H(5A) | 110.5 | O(2)-C(14)-C(17) | 109.16(11) |

| | | | |
|---|---|---|---|
| C(15)-C(14)-C(17) | 113.32(14) | C(14)-C(16)-H(16B) | 108.6(12) |
| O(2)-C(14)-C(16) | 101.29(12) | H(16A)-C(16)-H(16B) | 111.6(17) |
| C(15)-C(14)-C(16) | 110.45(13) | C(14)-C(16)-H(16C) | 110.0(13) |
| C(17)-C(14)-C(16) | 111.38(14) | H(16A)-C(16)-H(16C) | 108.3(17) |
| C(14)-C(15)-H(15A) | 114.2(13) | H(16B)-C(16)-H(16C) | 106.6(18) |
| C(14)-C(15)-H(15B) | 111.0(12) | C(14)-C(17)-H(17A) | 113.6(13) |
| H(15A)-C(15)-H(15B) | 105.6(18) | C(14)-C(17)-H(17B) | 108.2(14) |
| C(14)-C(15)-H(15C) | 108.8(11) | H(17A)-C(17)-H(17B) | 108.7(19) |
| H(15A)-C(15)-H(15C) | 107.9(17) | C(14)-C(17)-H(17C) | 113.5(12) |
| H(15B)-C(15)-H(15C) | 109.2(16) | H(17A)-C(17)-H(17C) | 106.9(17) |
| C(14)-C(16)-H(16A) | 111.6(10) | H(17B)-C(17)-H(17C) | 105.6(18) |

**Table A5**. Anisotropic displacement parameters ($Å^2$ x $10^3$) for $C_{17}H_{23}NO_5S$.The anisotropic
displacement factor exponent takes the form: $-2\pi^2[ h^2 a^{*2}U_{11} + ... + 2 h k a^* b^* U_{12} ]$

| | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| S | 19(1) | 20(1) | 18(1) | -1(1) | -2(1) | 3(1) |
| O(1) | 35(1) | 29(1) | 16(1) | -3(1) | -3(1) | -9(1) |
| O(2) | 23(1) | 22(1) | 15(1) | 2(1) | -1(1) | 5(1) |
| O(3) | 37(1) | 26(1) | 21(1) | -4(1) | 1(1) | 8(1) |
| O(4) | 35(1) | 25(1) | 21(1) | -6(1) | -4(1) | 6(1) |
| O(5) | 21(1) | 41(1) | 30(1) | -1(1) | -3(1) | 6(1) |
| N | 36(1) | 18(1) | 13(1) | -2(1) | -5(1) | 2(1) |
| C(1) | 23(1) | 22(1) | 25(1) | 1(1) | -2(1) | -1(1) |
| C(2) | 30(1) | 28(1) | 23(1) | 6(1) | 3(1) | -2(1) |
| C(3) | 33(1) | 29(1) | 15(1) | 3(1) | -2(1) | 0(1) |
| C(4) | 45(1) | 23(1) | 13(1) | -1(1) | -5(1) | -3(1) |
| C(5) | 61(1) | 51(1) | 18(1) | -1(1) | -4(1) | -30(1) |
| C(6) | 101(2) | 129(3) | 36(1) | -42(1) | 34(1) | -86(2) |
| C(7) | 44(1) | 42(1) | 29(1) | -14(1) | 10(1) | -23(1) |
| C(8) | 41(1) | 34(1) | 33(1) | -2(1) | -12(1) | 1(1) |
| C(9) | 52(1) | 31(1) | 38(1) | -14(1) | -3(1) | 9(1) |
| C(10) | 51(1) | 44(1) | 30(1) | -3(1) | -11(1) | -12(1) |
| C(11) | 35(1) | 55(1) | 57(1) | 8(1) | -13(1) | -3(1) |
| C(12) | 34(1) | 49(1) | 75(2) | -21(1) | 17(1) | -3(1) |
| C(13) | 21(1) | 18(1) | 18(1) | 0(1) | -1(1) | -2(1) |
| C(14) | 23(1) | 22(1) | 17(1) | 5(1) | -3(1) | 3(1) |
| C(15) | 31(1) | 21(1) | 27(1) | 4(1) | -2(1) | 0(1) |
| C(16) | 36(1) | 29(1) | 17(1) | 3(1) | -4(1) | -2(1) |
| C(17) | 23(1) | 32(1) | 31(1) | 8(1) | -3(1) | -1(1) |

**Table A6**. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$ x $10^3$ ) for $C_{17}H_{23}NO_5S$.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1A) | 2020(30) | 9328(17) | 1151(6) | 24(5) |
| H(1B) | 4080(40) | 8419(19) | 1228(7) | 35(5) |
| H(2) | 2770(40) | 8560(20) | 366(8) | 47(6) |
| H(3) | 1510(30) | 6803(16) | 190(7) | 24(4) |
| H(4) | 1970(30) | 5344(17) | 770(6) | 18(4) |
| H(5A) | -1844 | 4924 | 1004 | 52 |
| H(5B) | -2659 | 6193 | 797 | 52 |
| H(6A) | -4995 | 4867 | 347 | 107 |
| H(6B) | -3526 | 3675 | 455 | 107 |
| H(5'A) | -1480 | 4729 | 902 | 52 |
| H(5'B) | -2493 | 6031 | 975 | 52 |
| H(6'A) | -5167 | 4314 | 410 | 107 |
| H(6'B) | -2530 | 3797 | 397 | 107 |
| H(8) | -870(50) | 3080(20) | -315(7) | 48(6) |
| H(9) | -1610(40) | 2430(20) | -1076(8) | 48(6) |
| H(10) | -5060(40) | 2870(20) | -1489(9) | 56(7) |
| H(11) | -7940(60) | 4100(20) | -1091(9) | 72(8) |
| H(12) | -7240(50) | 4780(30) | -314(10) | 79(9) |
| H(15A) | 3910(40) | 3275(19) | 2055(7) | 34(5) |
| H(15B) | 1880(40) | 3530(17) | 2371(6) | 27(5) |
| H(15C) | 4420(40) | 3168(17) | 2589(7) | 28(5) |
| H(16A) | 3920(30) | 6296(17) | 2855(6) | 23(5) |
| H(16B) | 1970(40) | 5260(20) | 2898(7) | 35(6) |
| H(16C) | 4500(40) | 5041(19) | 3085(8) | 44(6) |
| H(17A) | 7380(40) | 4800(20) | 1927(8) | 46(6) |
| H(17B) | 7850(40) | 4760(20) | 2501(8) | 51(7) |
| H(17C) | 7290(30) | 5970(17) | 2250(6) | 25(5) |

**Table A7**. Torsion angles [°] for $C_{17}H_{23}NO_5S$.

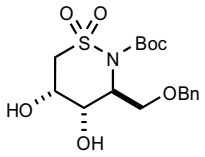
| | |
|---|---|
| O(4)-S-N-C(13) | -8.04(16) |
| O(5)-S-N-C(13) | -139.22(13) |
| C(1)-S-N-C(13) | 107.53(14) |
| O(4)-S-N-C(4) | -174.77(11) |
| O(5)-S-N-C(4) | 54.05(13) |
| C(1)-S-N-C(4) | -59.21(13) |
| O(4)-S-C(1)-C(2) | 164.30(11) |
| O(5)-S-C(1)-C(2) | -63.48(13) |
| N-S-C(1)-C(2) | 47.84(13) |
| S-C(1)-C(2)-C(3) | -22.1(2) |
| C(1)-C(2)-C(3)-C(4) | -3.7(3) |
| C(13)-N-C(4)-C(3) | -128.37(15) |
| S-N-C(4)-C(3) | 39.98(19) |
| C(13)-N-C(4)-C(5) | 102.66(18) |
| S-N-C(4)-C(5) | -88.99(16) |
| C(2)-C(3)-C(4)-N | -4.0(3) |
| C(2)-C(3)-C(4)-C(5) | 122.7(2) |
| C(6)-O(1)-C(5)-C(4) | 167.7(2) |
| N-C(4)-C(5)-O(1) | -167.73(14) |
| C(3)-C(4)-C(5)-O(1) | 64.0(2) |
| C(5)-O(1)-C(6)-C(7) | 171.8(2) |
| O(1)-C(6)-C(7)-C(12) | -123.2(3) |
| O(1)-C(6)-C(7)-C(8) | 58.5(4) |
| C(12)-C(7)-C(8)-C(9) | -0.2(3) |
| C(6)-C(7)-C(8)-C(9) | 178.1(2) |
| C(7)-C(8)-C(9)-C(10) | 0.2(3) |
| C(8)-C(9)-C(10)-C(11) | 0.6(3) |
| C(9)-C(10)-C(11)-C(12) | -1.3(3) |
| C(8)-C(7)-C(12)-C(11) | -0.4(3) |
| C(6)-C(7)-C(12)-C(11) | -178.8(2) |
| C(10)-C(11)-C(12)-C(7) | 1.2(3) |
| C(14)-O(2)-C(13)-O(3) | 7.8(2) |

| | |
|---|---|
| C(14)-O(2)-C(13)-N | -174.77(12) |
| C(4)-N-C(13)-O(3) | 10.0(2) |
| S-N-C(13)-O(3) | -156.79(13) |
| C(4)-N-C(13)-O(2) | -167.63(13) |
| S-N-C(13)-O(2) | 25.58(19) |
| C(13)-O(2)-C(14)-C(15) | -62.21(17) |
| C(13)-O(2)-C(14)-C(17) | 63.11(17) |
| C(13)-O(2)-C(14)-C(16) | -179.32(13) |

Crystal Structure Report

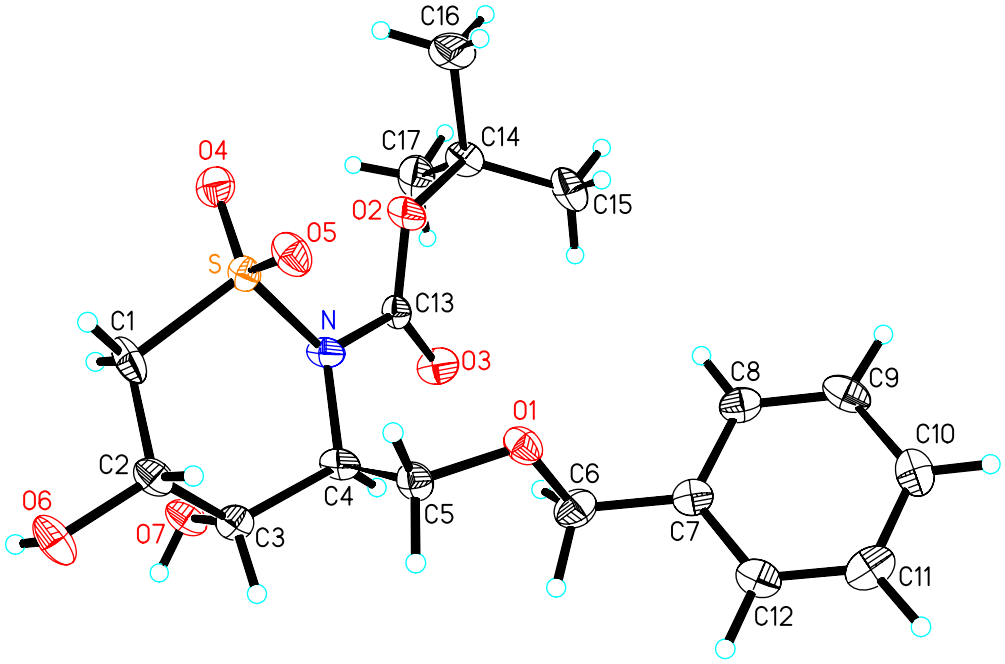
for

$C_{17}H_{25}NO_7S$




**2.9**

**Contents**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C14
O4
O2
C15
O5
S
C13
C1
N
O3
C8
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O1
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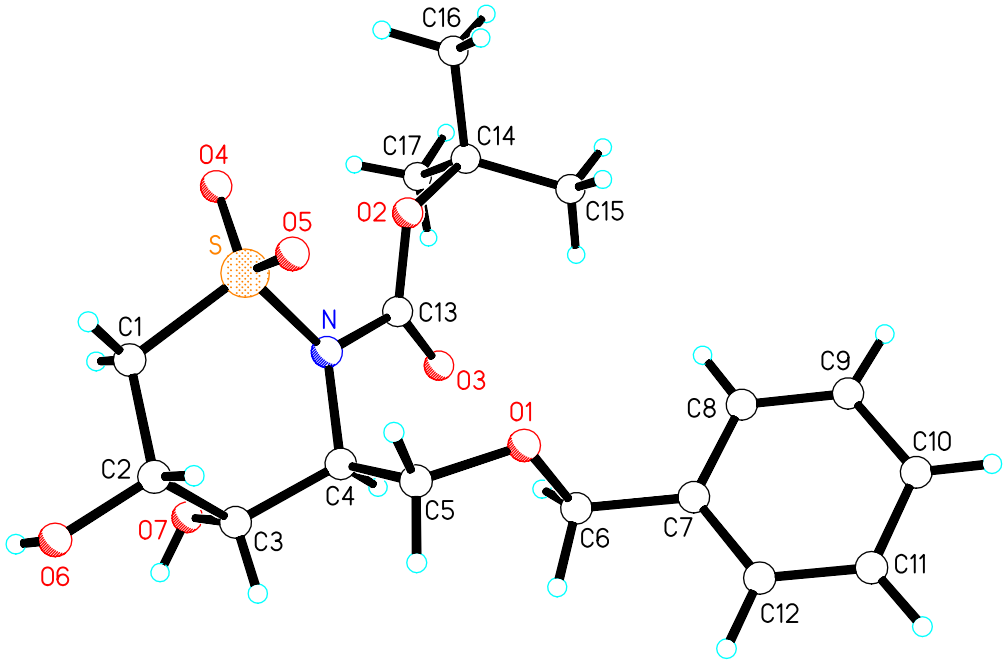
C4
C5
O6
O7
C3
C7
C11
C12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C17
C14
O4
O2
C15
O5
S
C1
N
C13
O3
C9
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O1
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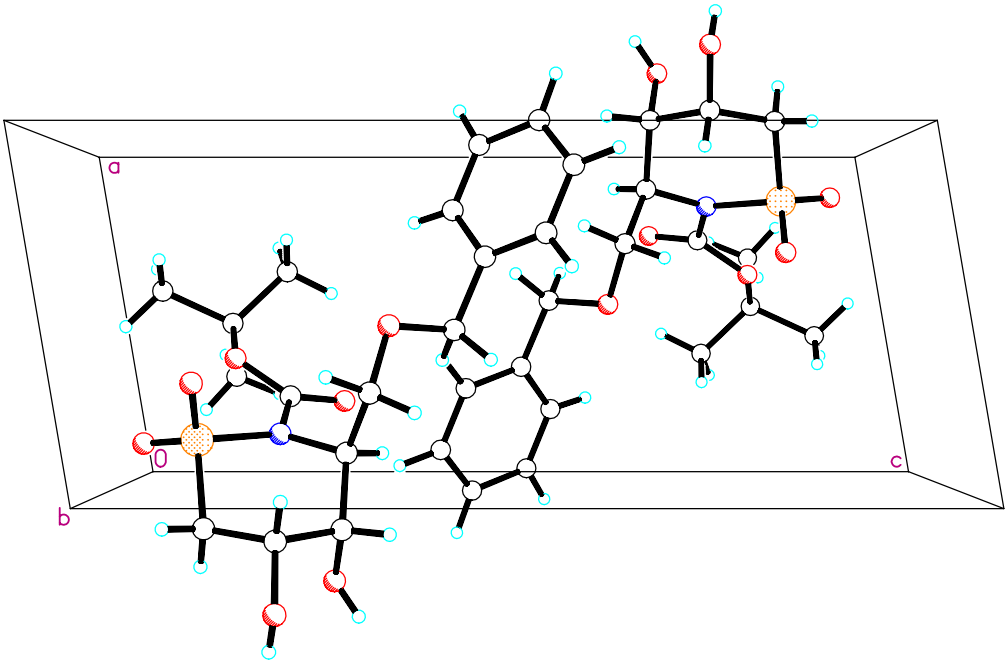
C5
C7
O7
C3
C6
C11
O6
C12


a
b
c
0

**Comments**

The asymmetric unit contains one $C_{17}H_{25}NO_7S$ molecule (**2.9**). All displacement ellipsoids are drawn at the 50% probability level.

**Brief Experimental Description to be Included as Text or as a Footnote at Time of Publication**

Colorless needle-shaped crystals of $C_{17}H_{25}NO_7S$ are, at 100(2) K, monoclinic, space group $P2_1 - C_2^2$ (No. 4) (1) with **a** = 6.556(1) Å, **b** = 9.379(2) Å, **c** = 15.518(3) Å, $\beta$ = 99.695(4)°, V = 940.5(3) $Å^3$ and Z = 2 molecules {$d_{calcd}$ = 1.368 $g/cm^3$; $\mu_a$(MoK$\alpha$) = 0.211 $mm^{-1}$}. A full hemisphere of diffracted intensities (1850 40-second frames with a $\omega$ scan width of 0.30°) was measured for a single-domain specimen using graphite-monochromated MoK$\alpha$ radiation ($\lambda$= 0.71073 Å) on a Bruker SMART APEX CCD Single Crystal Diffraction System (2). X-rays were provided by a fine-focus sealed x-ray tube operated at 50kV and 35mA. Lattice constants were determined with the Bruker SAINT software package using peak centers for 1602 reflections. A total of 8184 integrated reflection intensities having 2$\theta$((MoK$\alpha$)< 51.99° were produced using the Bruker program SAINT(3); 3690 of these were unique and gave $R_{int}$ = 0.084 with a coverage which was 99.9% complete. The data were corrected empirically for variable absorption effects using equivalent reflections; the relative transmission factors ranged from 0.751 to 1.000. The Bruker software package SHELXTL was used to solve the structure using "direct methods" techniques. All stages of weighted full-matrix least-squares refinement were conducted using $F_o^2$ data with the SHELXTL Version 6.10 software package(4).

The final structural model incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. All hydrogen atoms were located in a difference Fourier and included in the structural model as independent isotropic atoms whose positional parameters were allowed to vary in least-squares refinement cycles. The isotropic thermal parameters of all hydrogen atoms were fixed at values 1.2 (nonmethyl) or 1.5 (methyl) times the equivalent isotropic thermal parameter of the oxygen or carbon atom to which they are covalently bonded. A total of 310 parameters were refined using 1 restraint, 3690 data and weights of $w = 1/[\sigma^2(F^2) + (0.0464\ P)^2]$, where $P = [F_o^2 + 2F_c^2] / 3$. Final agreement factors at convergence are: $R_1$(unweighted, based on F) = 0.065 for 2892 independent absorption-corrected "observed" reflections having $2\theta(MoK\alpha) < 51.99°$ and $I > 2\sigma(I)$; $R_1$(unweighted, based on F) = 0.083 and $wR_2$(weighted, based on $F^2$) = 0.127 for all 3690 independent absorption-corrected reflections having $2\theta(MoK\alpha) < 51.99°$. The largest shift/s.u. was 0.000 in the final refinement cycle. The final difference map had maxima and minima of 0.61 and -0.56 $e^-/Å^3$, respectively. The absolute configuration was determined experimentally using anomalous dispersion of the x-rays; the "Flack" absolute structure parameter refined to a final value of –0.01(12).

**Acknowledgment**

The authors thank the National Science Foundation (grant CHE-0079282) and the University of Kansas for funds to purchase the x-ray instrument and computers.

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(7) Data Reduction: SAINT Software Reference Manual (1998). Bruker-AXS, 6300 Enterprise Dr., Madison, WI 53719-1173, USA.

(8) G. M. Sheldrick (2000). SHELXTL Version 6.10 Reference Manual. Bruker-AXS, 5465 E. Cheryl Parkway, Madison, WI 53711-5373 USA.

**Table A8**. Crystal data and structure refinement for $C_{17}H_{25}NO_7S$.

| | | |
|---|---|---|
| Empirical formula | $C_{17}H_{25}NO_7S$ | |
| Formula weight | 387.44 | |
| Temperature | 100(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | $P2_1 - C_2^2$ (No. 4) | |
| Unit cell dimensions | **a** = 6.556(1) Å | **α**= 90.000° |
| | **b** = 9.379(2) Å | **β**= 99.695(4)° |
| | **c** = 15.518(3) Å | **γ** = 90.000° |
| Volume | 940.5(3) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.368 $Mg/m^3$ | |
| Absorption coefficient | 0.211 $mm^{-1}$ | |
| F(000) | 412 | |
| Crystal size | 0.14 x 0.06 x 0.02 $mm^3$ | |
| 2Theta range for data collection | 2.55° to 25.99° | |
| Index ranges | $-8 \le h \le 8$, $-11 \le k \le 11$, $-19 \le l \le 19$ | |
| Reflections collected | 8184 | |
| Independent reflections | 3690 [$R_{int}$ = 0.084] | |
| Completeness to theta = 25.99° | 99.9 % | |
| Absorption correction | Empirical | |
| Max. and min. transmission | 1.000 and 0.751 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3690 / 1 / 310 | |
| Goodness-of-fit on $F^2$ | 1.016 | |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.065, $wR_2$ = 0.121 | |
| R indices (all data) | $R_1$ = 0.083, $wR_2$ = 0.127 | |
| Absolute structure parameter | -0.01(12) | |
| Largest diff. peak and hole | 0.61 and -0.56 $e^-/Å^3$ | |

---

$R_1 = \Sigma \, ||F_o| - |F_c|| \, / \, \Sigma \, |F_o|$

$wR_2 = \{ \, \Sigma \, [w(F_o^2 - F_c^2)^2] \, / \, \Sigma \, [w(F_o^2)^2] \, \}^{1/2}$

**Table A9**. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters (Å$^2$ x $10^3$) for $C_{17}H_{25}NO_7S$. U(eq) is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| S | 1469(2) | 6024(1) | 1155(1) | 18(1) |
| O(1) | 4685(4) | 6036(4) | 3631(2) | 22(1) |
| O(2) | 3701(5) | 3506(3) | 1594(2) | 21(1) |
| O(3) | 2406(5) | 3013(3) | 2827(2) | 26(1) |
| O(4) | 1293(5) | 5103(3) | 433(2) | 26(1) |
| O(5) | 3103(5) | 7062(3) | 1283(2) | 25(1) |
| O(6) | -3034(5) | 8385(3) | 1876(2) | 29(1) |
| O(7) | -2587(5) | 5510(3) | 2455(2) | 24(1) |
| N | 1570(6) | 5079(4) | 2083(2) | 20(1) |
| C(1) | -915(7) | 6931(5) | 1129(4) | 25(1) |
| C(2) | -1167(8) | 7658(5) | 1976(3) | 21(1) |
| C(3) | -995(7) | 6529(4) | 2698(3) | 19(1) |
| C(4) | 1078(7) | 5798(4) | 2869(3) | 18(1) |
| C(5) | 2823(7) | 6761(5) | 3296(3) | 21(1) |
| C(6) | 4557(8) | 5166(6) | 4376(3) | 27(1) |
| C(7) | 6665(7) | 4935(5) | 4891(3) | 21(1) |
| C(8) | 8065(8) | 3983(5) | 4591(3) | 23(1) |
| C(9) | 10002(9) | 3809(5) | 5052(4) | 26(1) |
| C(10) | 10650(8) | 4537(5) | 5827(3) | 25(1) |
| C(11) | 9270(8) | 5452(5) | 6133(3) | 27(1) |
| C(12) | 7320(8) | 5641(5) | 5663(3) | 24(1) |
| C(13) | 2584(7) | 3746(4) | 2207(3) | 16(1) |
| C(14) | 4728(7) | 2091(5) | 1539(3) | 25(1) |
| C(15) | 6311(8) | 1856(5) | 2329(4) | 28(1) |
| C(16) | 5713(10) | 2296(6) | 734(4) | 35(1) |
| C(17) | 3062(9) | 943(7) | 1390(4) | 34(1) |

**Table A10**. Bond lengths [Å] for $C_{17}H_{25}NO_7S$.

| | | | |
|---|---|---|---|
| S-O(4) | 1.405(3) | C(6)-C(7) | 1.491(7) |
| S-O(5) | 1.437(3) | C(6)-H(6A) | 1.07(5) |
| S-N | 1.682(4) | C(6)-H(6B) | 1.04(5) |
| S-C(1) | 1.774(5) | C(7)-C(12) | 1.372(7) |
| O(1)-C(5) | 1.417(5) | C(7)-C(8) | 1.415(7) |
| O(1)-C(6) | 1.429(6) | C(8)-C(9) | 1.358(7) |
| O(2)-C(13) | 1.314(5) | C(8)-H(8) | 0.85(5) |
| O(2)-C(14) | 1.497(5) | C(9)-C(10) | 1.385(7) |
| O(3)-C(13) | 1.205(5) | C(9)-H(9) | 0.94(5) |
| O(6)-C(2) | 1.387(6) | C(10)-C(11) | 1.388(7) |
| O(6)-H(6O) | 0.78(6) | C(10)-H(10) | 0.93(6) |
| O(7)-C(3) | 1.418(5) | C(11)-C(12) | 1.373(7) |
| O(7)-H(7O) | 0.81(5) | C(11)-H(11) | 0.95(5) |
| N-C(13) | 1.414(5) | C(12)-H(12) | 1.00(5) |
| N-C(4) | 1.477(5) | C(14)-C(15) | 1.484(7) |
| C(1)-C(2) | 1.514(7) | C(14)-C(16) | 1.512(7) |
| C(1)-H(1A) | 1.04(5) | C(14)-C(17) | 1.523(8) |
| C(1)-H(1B) | 0.85(5) | C(15)-H(15A) | 0.94(6) |
| C(2)-C(3) | 1.532(6) | C(15)-H(15B) | 0.85(6) |
| C(2)-H(2) | 0.93(5) | C(15)-H(15C) | 0.98(5) |
| C(3)-C(4) | 1.506(6) | C(16)-H(16A) | 0.89(6) |
| C(3)-H(3) | 0.94(5) | C(16)-H(16B) | 0.93(7) |
| C(4)-C(5) | 1.520(6) | C(16)-H(16C) | 1.00(6) |
| C(4)-H(4) | 1.00(5) | C(17)-H(17A) | 0.91(6) |
| C(5)-H(5A) | 0.99(5) | C(17)-H(17B) | 1.03(6) |
| C(5)-H(5B) | 0.99(5) | C(17)-H(17C) | 0.93(6) |

**Table A11**. Bond angles [°] for $C_{17}H_{25}NO_7S$.

| | | | |
|---|---|---|---|
| O(4)-S-O(5) | 119.0(2) | N-C(4)-C(5) | 112.2(4) |
| O(4)-S-N | 110.19(18) | C(3)-C(4)-C(5) | 113.4(3) |
| O(5)-S-N | 108.6(2) | N-C(4)-H(4) | 100(3) |
| O(4)-S-C(1) | 108.9(2) | C(3)-C(4)-H(4) | 109(3) |
| O(5)-S-C(1) | 108.2(2) | C(5)-C(4)-H(4) | 109(3) |
| N-S-C(1) | 100.4(2) | O(1)-C(5)-C(4) | 114.4(4) |
| C(5)-O(1)-C(6) | 114.0(4) | O(1)-C(5)-H(5A) | 101(3) |
| C(13)-O(2)-C(14) | 120.3(3) | C(4)-C(5)-H(5A) | 110(3) |
| C(2)-O(6)-H(6O) | 123(4) | O(1)-C(5)-H(5B) | 109(3) |
| C(3)-O(7)-H(7O) | 107(4) | C(4)-C(5)-H(5B) | 106(3) |
| C(13)-N-C(4) | 117.0(4) | H(5A)-C(5)-H(5B) | 117(4) |
| C(13)-N-S | 122.2(3) | O(1)-C(6)-C(7) | 110.0(4) |
| C(4)-N-S | 119.0(3) | O(1)-C(6)-H(6A) | 108(3) |
| C(2)-C(1)-S | 114.9(4) | C(7)-C(6)-H(6A) | 117(3) |
| C(2)-C(1)-H(1A) | 110(2) | O(1)-C(6)-H(6B) | 105(3) |
| S-C(1)-H(1A) | 107(3) | C(7)-C(6)-H(6B) | 108(3) |
| C(2)-C(1)-H(1B) | 116(3) | H(6A)-C(6)-H(6B) | 108(4) |
| S-C(1)-H(1B) | 99(3) | C(12)-C(7)-C(8) | 117.8(4) |
| H(1A)-C(1)-H(1B) | 109(4) | C(12)-C(7)-C(6) | 121.5(5) |
| O(6)-C(2)-C(1) | 110.4(4) | C(8)-C(7)-C(6) | 120.6(4) |
| O(6)-C(2)-C(3) | 112.1(4) | C(9)-C(8)-C(7) | 120.2(5) |
| C(1)-C(2)-C(3) | 108.5(4) | C(9)-C(8)-H(8) | 121(4) |
| O(6)-C(2)-H(2) | 113(3) | C(7)-C(8)-H(8) | 118(4) |
| C(1)-C(2)-H(2) | 109(3) | C(8)-C(9)-C(10) | 121.4(5) |
| C(3)-C(2)-H(2) | 104(3) | C(8)-C(9)-H(9) | 126(3) |
| O(7)-C(3)-C(4) | 110.0(3) | C(10)-C(9)-H(9) | 112(3) |
| O(7)-C(3)-C(2) | 108.2(4) | C(9)-C(10)-C(11) | 118.7(5) |
| C(4)-C(3)-C(2) | 113.4(4) | C(9)-C(10)-H(10) | 123(3) |
| O(7)-C(3)-H(3) | 110(3) | C(11)-C(10)-H(10) | 119(3) |
| C(4)-C(3)-H(3) | 102(3) | C(12)-C(11)-C(10) | 120.0(5) |
| C(2)-C(3)-H(3) | 114(3) | C(12)-C(11)-H(11) | 123(3) |
| N-C(4)-C(3) | 112.2(4) | C(10)-C(11)-H(11) | 117(3) |

| | | | |
|---|---|---|---|
| C(7)-C(12)-C(11) | 121.9(5) | C(14)-C(15)-H(15C) | 110(3) |
| C(7)-C(12)-H(12) | 119(3) | H(15A)-C(15)-H(15C) | 107(4) |
| C(11)-C(12)-H(12) | 119(3) | H(15B)-C(15)-H(15C) | 114(5) |
| O(3)-C(13)-O(2) | 128.4(4) | C(14)-C(16)-H(16A) | 111(4) |
| O(3)-C(13)-N | 120.5(4) | C(14)-C(16)-H(16B) | 108(3) |
| O(2)-C(13)-N | 111.1(4) | H(16A)-C(16)-H(16B) | 108(5) |
| C(15)-C(14)-O(2) | 110.0(4) | C(14)-C(16)-H(16C) | 111(3) |
| C(15)-C(14)-C(16) | 111.4(5) | H(16A)-C(16)-H(16C) | 114(5) |
| O(2)-C(14)-C(16) | 101.2(4) | H(16B)-C(16)-H(16C) | 105(5) |
| C(15)-C(14)-C(17) | 113.9(4) | C(14)-C(17)-H(17A) | 111(4) |
| O(2)-C(14)-C(17) | 108.5(4) | C(14)-C(17)-H(17B) | 109(3) |
| C(16)-C(14)-C(17) | 111.1(4) | H(17A)-C(17)-H(17B) | 108(5) |
| C(14)-C(15)-H(15A) | 108(3) | C(14)-C(17)-H(17C) | 110(4) |
| C(14)-C(15)-H(15B) | 115(4) | H(17A)-C(17)-H(17C) | 111(5) |
| H(15A)-C(15)-H(15B) | 102(5) | H(17B)-C(17)-H(17C) | 108(5) |

**Table A12**. Anisotropic displacement parameters ($Å^2$ x $10^3$) for $C_{17}H_{25}NO_7S$. The anisotropic displacement factor exponent takes the form: $-2\pi^2[ h^2 a^{*2}U_{11} + ... + 2 h k a^* b^* U_{12} ]$

| | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| S | 20(1) | 12(1) | 21(1) | 5(1) | 4(1) | 3(1) |
| O(1) | 21(2) | 20(2) | 28(2) | 4(2) | 8(1) | 3(2) |
| O(2) | 26(2) | 9(2) | 28(2) | 1(1) | 10(2) | 8(1) |
| O(3) | 40(2) | 13(2) | 25(2) | 7(2) | 9(2) | 4(2) |
| O(4) | 31(2) | 22(2) | 25(2) | 4(2) | 5(2) | 4(2) |
| O(5) | 22(2) | 19(2) | 34(2) | 7(1) | 7(2) | 4(1) |
| O(6) | 20(2) | 17(2) | 50(2) | -4(2) | 6(2) | 3(1) |
| O(7) | 21(2) | 17(2) | 35(2) | -4(1) | 10(2) | -1(1) |
| N | 28(2) | 13(2) | 20(2) | 5(2) | 11(2) | 7(2) |
| C(1) | 15(2) | 19(3) | 42(3) | 12(2) | 7(2) | 5(2) |
| C(2) | 21(3) | 14(2) | 30(3) | -3(2) | 6(2) | 1(2) |
| C(3) | 22(3) | 13(2) | 23(2) | -6(2) | 3(2) | -4(2) |
| C(4) | 27(2) | 4(2) | 23(2) | -2(2) | 9(2) | 2(2) |
| C(5) | 22(3) | 14(2) | 26(3) | -2(2) | 3(2) | 2(2) |
| C(6) | 32(3) | 28(3) | 22(3) | 2(2) | 6(2) | -5(2) |
| C(7) | 27(3) | 14(2) | 22(2) | 4(2) | 7(2) | -3(2) |
| C(8) | 30(3) | 17(2) | 24(3) | -4(2) | 7(2) | -5(2) |
| C(9) | 29(3) | 14(3) | 39(3) | 4(2) | 17(2) | 5(2) |
| C(10) | 23(3) | 20(2) | 33(3) | 12(2) | 4(2) | -2(2) |
| C(11) | 44(3) | 11(2) | 25(3) | 1(2) | 6(2) | -7(2) |
| C(12) | 28(3) | 13(2) | 31(3) | 2(2) | 11(2) | 0(2) |
| C(13) | 18(3) | 10(2) | 20(2) | -1(2) | 1(2) | 2(2) |
| C(14) | 35(3) | 10(2) | 28(3) | -7(2) | 6(2) | 14(2) |
| C(15) | 24(3) | 13(3) | 45(3) | -6(2) | 3(2) | 8(2) |
| C(16) | 44(4) | 28(3) | 33(3) | -8(3) | 13(3) | 14(3) |
| C(17) | 37(3) | 25(3) | 37(3) | -9(3) | -2(2) | 10(3) |

**Table A13**. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$ x $10^3$) for $C_{17}H_{25}NO_7S$.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(6O) | -4100(90) | 8020(60) | 1720(40) | 34 |
| H(7O) | -3560(80) | 5750(50) | 2680(30) | 28 |
| H(1A) | -2080(70) | 6190(60) | 950(30) | 30 |
| H(1B) | -860(80) | 7480(60) | 700(30) | 30 |
| H(2) | -30(80) | 8240(50) | 2150(30) | 26 |
| H(3) | -1080(70) | 6900(50) | 3250(30) | 23 |
| H(4) | 1000(70) | 4950(50) | 3260(30) | 21 |
| H(5A) | 3280(70) | 7390(50) | 2850(30) | 25 |
| H(5B) | 2300(70) | 7240(50) | 3790(30) | 25 |
| H(6A) | 3670(80) | 4240(50) | 4160(30) | 32 |
| H(6B) | 3720(70) | 5780(50) | 4760(30) | 32 |
| H(8) | 7710(80) | 3600(60) | 4090(30) | 28 |
| H(9) | 11070(80) | 3260(60) | 4880(30) | 32 |
| H(10) | 12010(80) | 4490(50) | 6130(30) | 30 |
| H(11) | 9730(70) | 5880(60) | 6690(30) | 32 |
| H(12) | 6350(70) | 6320(50) | 5890(30) | 28 |
| H(15A) | 7070(80) | 1040(70) | 2230(30) | 41 |
| H(15B) | 7250(90) | 2490(60) | 2420(30) | 41 |
| H(15C) | 5650(90) | 1660(60) | 2830(40) | 41 |
| H(16A) | 6640(90) | 3000(70) | 810(40) | 52 |
| H(16B) | 6400(90) | 1460(70) | 640(40) | 52 |
| H(16C) | 4630(100) | 2400(60) | 200(40) | 52 |
| H(17A) | 2040(90) | 1180(70) | 940(40) | 51 |
| H(17B) | 3710(100) | 0(70) | 1230(40) | 51 |
| H(17C) | 2520(90) | 790(70) | 1900(40) | 51 |

**Table A14**. Torsion angles [°] for $C_{17}H_{25}NO_7S$.

| | |
|---|---|
| O(4)-S-N-C(13) | 35.7(4) |
| O(5)-S-N-C(13) | -96.3(4) |
| C(1)-S-N-C(13) | 150.4(4) |
| O(4)-S-N-C(4) | -160.3(3) |
| O(5)-S-N-C(4) | 67.7(4) |
| C(1)-S-N-C(4) | -45.7(4) |
| O(4)-S-C(1)-C(2) | 164.6(3) |
| O(5)-S-C(1)-C(2) | -64.7(4) |
| N-S-C(1)-C(2) | 48.9(4) |
| S-C(1)-C(2)-O(6) | 177.5(3) |
| S-C(1)-C(2)-C(3) | -59.4(5) |
| O(6)-C(2)-C(3)-O(7) | 62.1(5) |
| C(1)-C(2)-C(3)-O(7) | -60.0(5) |
| O(6)-C(2)-C(3)-C(4) | -175.6(4) |
| C(1)-C(2)-C(3)-C(4) | 62.2(5) |
| C(13)-N-C(4)-C(3) | -141.5(4) |
| S-N-C(4)-C(3) | 53.7(4) |
| C(13)-N-C(4)-C(5) | 89.5(5) |
| S-N-C(4)-C(5) | -75.3(4) |
| O(7)-C(3)-C(4)-N | 62.5(5) |
| C(2)-C(3)-C(4)-N | -58.8(5) |
| O(7)-C(3)-C(4)-C(5) | -169.1(4) |
| C(2)-C(3)-C(4)-C(5) | 69.7(5) |
| C(6)-O(1)-C(5)-C(4) | -69.1(5) |
| N-C(4)-C(5)-O(1) | -64.2(5) |
| C(3)-C(4)-C(5)-O(1) | 167.4(4) |
| C(5)-O(1)-C(6)-C(7) | -157.0(4) |
| O(1)-C(6)-C(7)-C(12) | 104.4(5) |
| O(1)-C(6)-C(7)-C(8) | -75.0(6) |
| C(12)-C(7)-C(8)-C(9) | -1.3(7) |
| C(6)-C(7)-C(8)-C(9) | 178.1(5) |
| C(7)-C(8)-C(9)-C(10) | 0.8(7) |

| | |
|---|---|
| C(8)-C(9)-C(10)-C(11) | 0.5(7) |
| C(9)-C(10)-C(11)-C(12) | -1.2(7) |
| C(8)-C(7)-C(12)-C(11) | 0.6(6) |
| C(6)-C(7)-C(12)-C(11) | -178.9(4) |
| C(10)-C(11)-C(12)-C(7) | 0.7(7) |
| C(14)-O(2)-C(13)-O(3) | 8.7(7) |
| C(14)-O(2)-C(13)-N | -173.3(4) |
| C(4)-N-C(13)-O(3) | 25.3(6) |
| S-N-C(13)-O(3) | -170.4(3) |
| C(4)-N-C(13)-O(2) | -152.8(4) |
| S-N-C(13)-O(2) | 11.5(5) |
| C(13)-O(2)-C(14)-C(15) | -64.6(5) |
| C(13)-O(2)-C(14)-C(16) | 177.6(4) |
| C(13)-O(2)-C(14)-C(17) | 60.6(5) |

**Table A15**. Hydrogen bonds for $C_{17}H_{25}NO_7S$ [Å and °].

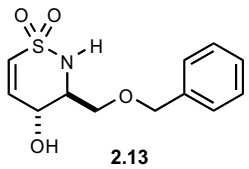
| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| O(6)-H(6O)...O(5)#1 | 0.78(6) | 2.05(6) | 2.831(5) | 179(6) |
| O(7)-H(7O)...O(1)#1 | 0.81(5) | 2.04(5) | 2.805(4) | 159(5) |

Symmetry transformations used to generate equivalent atoms: #1: x-1, y, z.

Crystal Structure Report

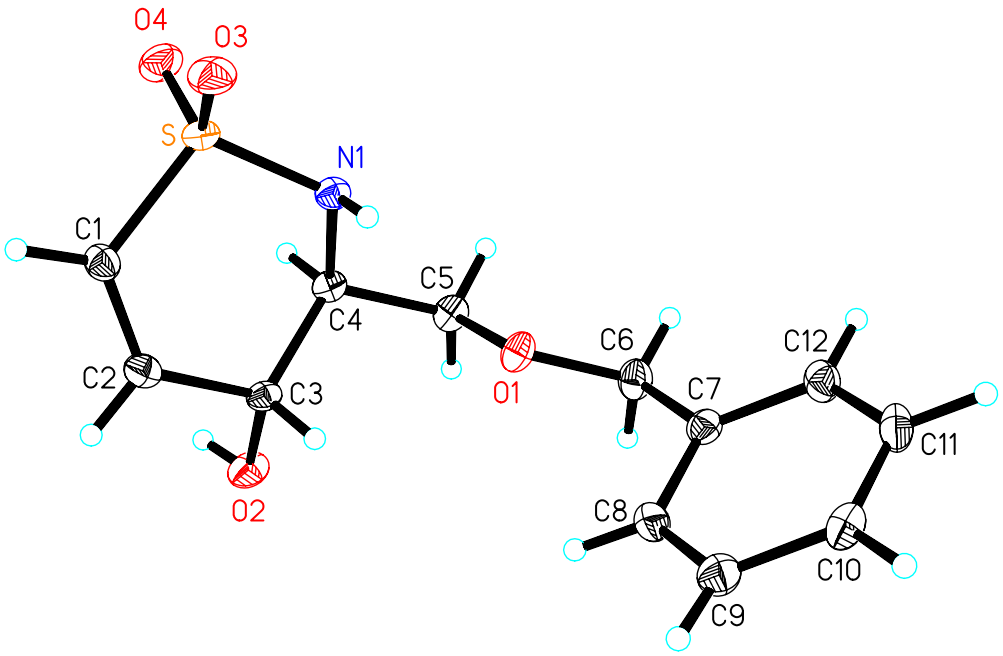
for

**$C_{12}H_{15}NO_4S$**




**2.13**

**Contents**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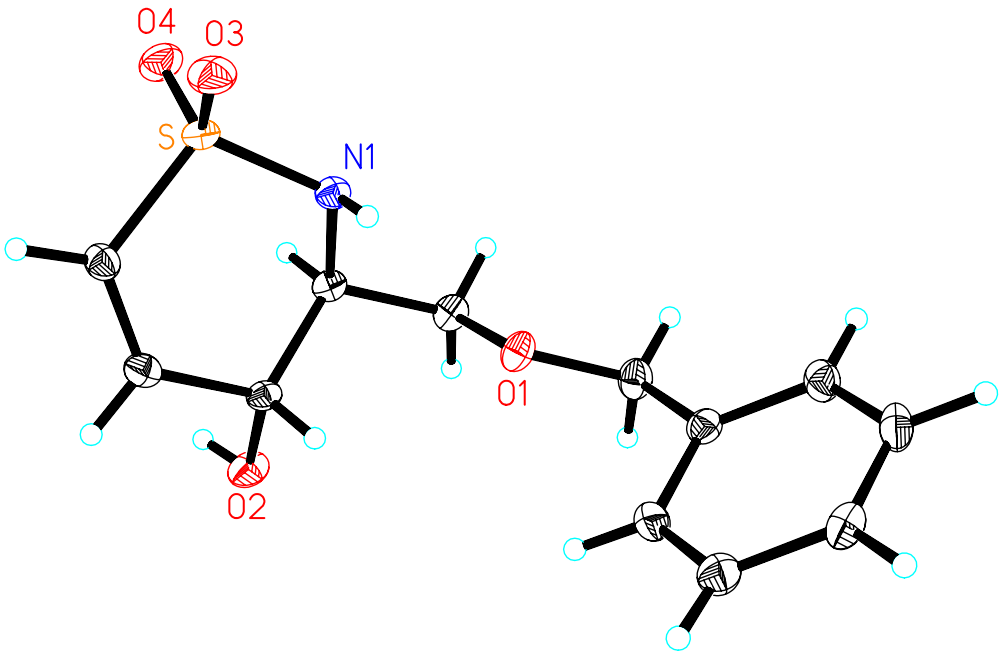
O3
S
N1
C1
C5
C4
C6
C12
O1
C2
C3
C7
C11
O2
C8
C10
C9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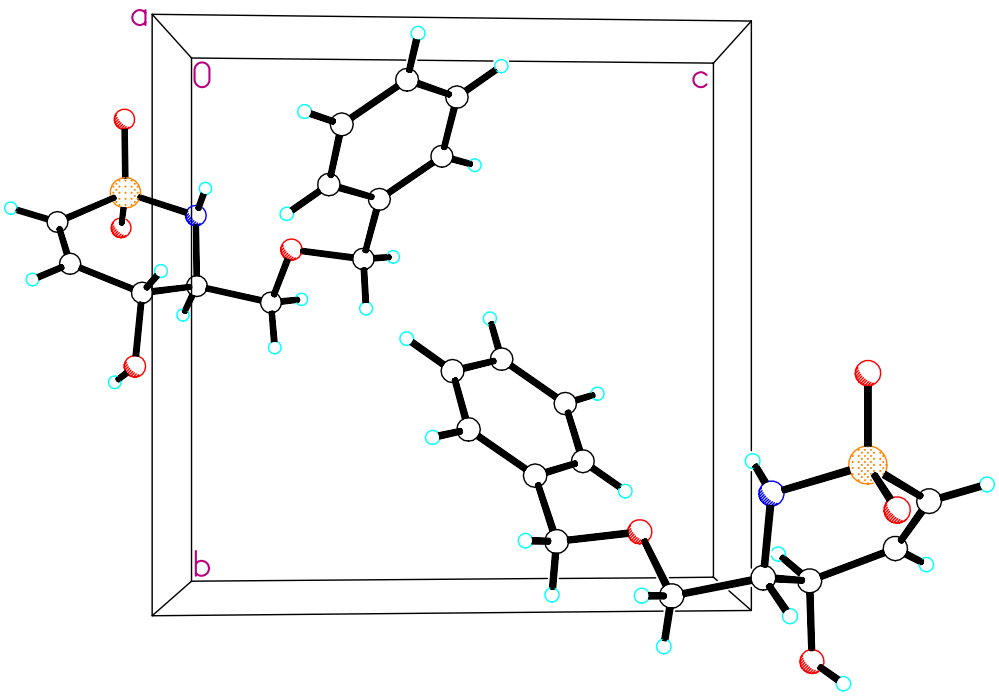
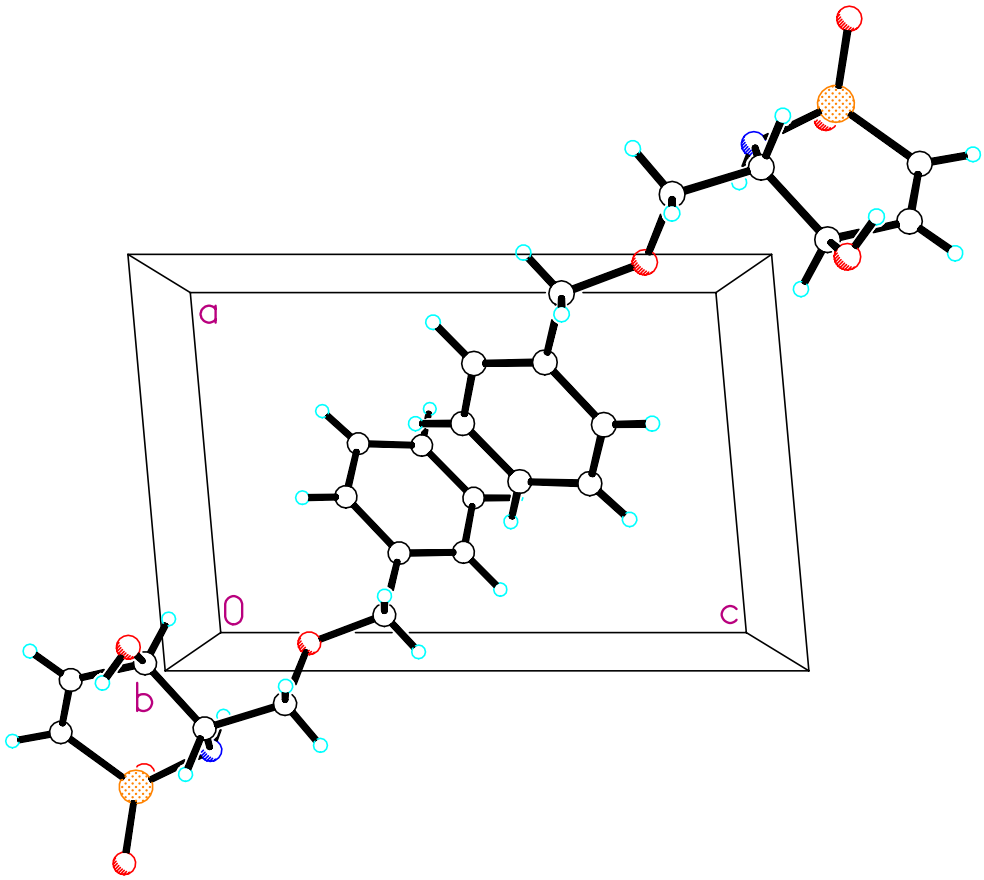
O3
S
N1
O1
O2


a
0
c
b


a
0
c
b

**Comments**

The asymmetric unit contains one $C_{12}H_{15}NO_4S$ molecule (**2.13**). All displacement ellipsoids are drawn at the 50% probability level.

**Brief Experimental Description to be Included as Text or as a Footnote at Time of Publication**

Colorless crystals of $C_{12}H_{15}NO_4S$ are, at 100(2) K, monoclinic, space group $P2_1 - C_2^2$ (No. 4) with **a** = 6.406(1) Å, **b** = 9.788(1) Å, **c** = 9.865(1) Å, **β** = 95.112(2)°, V = 616.1(1) $Å^3$ and Z = 2 molecules {$d_{calcd}$ = 1.452g/$cm^3$; $\mu_a$(MoKα) = 0.269 $mm^{-1}$}. A full hemisphere of diffracted intensities (1850 10-second frames with a ω scan width of 0.30°) was measured for a single-domain specimen using graphite-monochromated MoKα radiation (λ= 0.71073 Å) on a Bruker SMART APEX CCD Single Crystal Diffraction System (2). X-rays were provided by a fine-focus sealed x-ray tube operated at 50kV and 30mA. Lattice constants were determined with the Bruker SAINT software package using peak centers for 3642 reflections. A total 7585 integrated reflection intensities having 2θ((MoKα)< 61.00° were produced using the Bruker program SAINT(3); 3673 of these were unique and gave $R_{int}$ = 0.037 with a coverage which was 99.5% complete. The data were corrected empirically for variable absorption effects using equivalent reflections; the relative transmission factors ranged from 0.964 to 1.000. The Bruker software package SHELXTL was used to solve the structure using "direct methods" techniques. All stages of weighted full-matrix least-squares refinement were conducted using $F_o^2$ data with the SHELXTL Version 6.10 software package(4).

The final structural model incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. All hydrogen atoms were located in a difference Fourier and included in the structural model as independent isotropic atoms whose parameters were allowed to vary in least-squares refinement cycles. A total of 223 parameters were refined using 1 restraint, 3673 data and weights of $w = 1/ [\sigma^2(F^2) + (0.0483\ P)^2]$, where $P = [F_o^2 + 2F_c^2] / 3$. Final agreement factors at convergence are: $R_1$(unweighted, based on F) = 0.039 for 3532 independent absorption-corrected "observed" reflections having $2\theta(MoK\alpha) < 61.00°$ and $I > 2\sigma(I)$; $R_1$(unweighted, based on F) = 0.040 and $wR_2$(weighted, based on $F^2$) = 0.088 for all 3673 independent absorption-corrected reflections having $2\theta(MoK\alpha) < 61.00°$. The largest shift/s.u. was 0.000 in the final refinement cycle. The final difference map had maxima and minima of 0.58 and -0.25 $e^-/Å^3$, respectively.

**Acknowledgment**

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**References**

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**Table A16**. Crystal data and structure refinement for $C_{12}H_{15}NO_4S$.

| | | |
|---|---|---|
| Empirical formula | $C_{12}H_{15}NO_4S$ | |
| Formula weight | 269.31 | |
| Temperature | 100(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Monoclinic | |
| Space group | $P2_1 - C_2^2$ (No. 4) | |
| Unit cell dimensions | **a** = 6.406(1) Å | **α** = 90.000° |
| | **b** = 9.788(1) Å | **β** = 95.112(2)° |
| | **c** = 9.865(1) Å | **γ** = 90.000° |
| Volume | 616.1(1) $Å^3$ | |
| Z | 2 | |
| Density (calculated) | 1.452 $Mg/m^3$ | |
| Absorption coefficient | 0.269 $mm^{-1}$ | |
| F(000) | 284 | |
| Crystal size | 0.32 x 0.22 x 0.05 $mm^3$ | |
| Theta range for data collection | 2.94 to 30.50° | |
| Index ranges | $-8 \le h \le 9$, $-13 \le k \le 13$, $-13 \le l \le 13$ | |
| Reflections collected | 7585 | |
| Independent reflections | 3673 [$R_{int}$ = 0.037] | |
| Completeness to theta = 30.50° | 99.5 % | |
| Absorption correction | Empirical | |
| Max. and min. transmission | 1.000 and 0.964 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3673 / 1 / 223 | |
| Goodness-of-fit on $F^2$ | 1.024 | |
| Final R indices [I>2sigma(I)] | $R_1$ = 0.039, $wR_2$ = 0.088 | |
| R indices (all data) | $R_1$ = 0.040, $wR_2$ = 0.088 | |
| Absolute structure parameter | 0.05(6) | |
| Largest diff. peak and hole | 0.58 and -0.25 $e^-/Å^3$ | |

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$R_1 = \Sigma \, ||F_o| - |F_c|| \, / \, \Sigma \, |F_o|$

$wR_2 = \{ \Sigma [w(F_o^2 - F_c^2)^2] / \Sigma [w(F_o^2)^2] \}^{1/}$

**Table A17**. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$ x $10^3$) for $C_{12}H_{15}NO_4S$. U(eq) is defined as one third of the trace of the orthogonalized $U_{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| S | -4116(1) | 2422(1) | -1569(1) | 15(1) |
| O(1) | 44(2) | 3656(1) | 1890(1) | 17(1) |
| O(2) | 156(2) | 5891(1) | -1050(1) | 21(1) |
| O(3) | -4016(2) | 953(1) | -1581(1) | 22(1) |
| O(4) | -6124(2) | 3066(2) | -1819(1) | 23(1) |
| N(1) | -3007(2) | 2910(2) | -107(2) | 15(1) |
| C(1) | -2489(3) | 3067(2) | -2751(2) | 17(1) |
| C(2) | -936(3) | 3919(2) | -2362(2) | 17(1) |
| C(3) | -416(3) | 4482(2) | -958(2) | 14(1) |
| C(4) | -2200(3) | 4323(2) | -36(2) | 14(1) |
| C(5) | -1490(3) | 4653(2) | 1434(2) | 17(1) |
| C(6) | 835(3) | 3849(2) | 3273(2) | 19(1) |
| C(7) | 2474(3) | 2774(2) | 3605(2) | 16(1) |
| C(8) | 4042(3) | 2570(2) | 2724(2) | 19(1) |
| C(9) | 5543(3) | 1557(2) | 2997(2) | 21(1) |
| C(10) | 5498(3) | 747(2) | 4154(2) | 20(1) |
| C(11) | 3976(3) | 954(2) | 5039(2) | 21(1) |
| C(12) | 2458(3) | 1965(2) | 4762(2) | 19(1) |

**Table A18**. Bond lengths [Å] for $C_{12}H_{15}NO_4S$.

| | | | |
|---|---|---|---|
| S-O(4) | 1.434(1) | C(4)-H(4) | 0.96(2) |
| S-O(3) | 1.439(1) | C(5)-H(5A) | 0.94(2) |
| S-N(1) | 1.622(2) | C(5)-H(5B) | 0.94(2) |
| S-C(1) | 1.749(2) | C(6)-C(7) | 1.502(2) |
| O(1)-C(6) | 1.425(2) | C(6)-H(6A) | 0.88(2) |
| O(1)-C(5) | 1.428(2) | C(6)-H(6B) | 1.00(3) |
| O(2)-C(3) | 1.432(2) | C(7)-C(12) | 1.390(2) |
| O(2)-H(2O) | 0.76(3) | C(7)-C(8) | 1.400(2) |
| N(1)-C(4) | 1.476(2) | C(8)-C(9) | 1.391(3) |
| N(1)-H(1N) | 0.77(3) | C(8)-H(8) | 0.91(3) |
| C(1)-C(2) | 1.328(2) | C(9)-C(10) | 1.391(3) |
| C(1)-H(1) | 0.96(2) | C(9)-H(9) | 0.91(2) |
| C(2)-C(3) | 1.500(2) | C(10)-C(11) | 1.381(3) |
| C(2)-H(2) | 0.90(2) | C(10)-H(10) | 1.01(2) |
| C(3)-C(4) | 1.530(2) | C(11)-C(12) | 1.397(3) |
| C(3)-H(3) | 0.91(2) | C(11)-H(11) | 0.98(2) |
| C(4)-C(5) | 1.515(2) | C(12)-H(12) | 0.95(2) |

**Table A19**. Bond angles [°] for $C_{12}H_{15}NO_4S$.

| | | | |
|---|---|---|---|
| O(4)-S-O(3) | 118.49(8) | O(1)-C(5)-H(5B) | 109.9(13) |
| O(4)-S-N(1) | 109.82(8) | C(4)-C(5)-H(5B) | 112.1(13) |
| O(3)-S-N(1) | 106.57(8) | H(5A)-C(5)-H(5B) | 109.2(18) |
| O(4)-S-C(1) | 107.79(8) | O(1)-C(6)-C(7) | 107.36(14) |
| O(3)-S-C(1) | 108.99(8) | O(1)-C(6)-H(6A) | 110.9(14) |
| N(1)-S-C(1) | 104.28(8) | C(7)-C(6)-H(6A) | 110.8(15) |
| C(6)-O(1)-C(5) | 112.76(13) | O(1)-C(6)-H(6B) | 106.4(13) |
| C(3)-O(2)-H(2O) | 104(2) | C(7)-C(6)-H(6B) | 112.7(14) |
| C(4)-N(1)-S | 116.21(12) | H(6A)-C(6)-H(6B) | 109(2) |
| C(4)-N(1)-H(1N) | 109.8(19) | C(12)-C(7)-C(8) | 119.10(16) |
| S-N(1)-H(1N) | 109.8(19) | C(12)-C(7)-C(6) | 121.51(16) |
| C(2)-C(1)-S | 120.65(14) | C(8)-C(7)-C(6) | 119.38(15) |
| C(2)-C(1)-H(1) | 121.9(12) | C(9)-C(8)-C(7) | 120.22(16) |
| S-C(1)-H(1) | 117.5(12) | C(9)-C(8)-H(8) | 121.7(16) |
| C(1)-C(2)-C(3) | 126.56(16) | C(7)-C(8)-H(8) | 118.0(16) |
| C(1)-C(2)-H(2) | 119.3(13) | C(8)-C(9)-C(10) | 120.05(17) |
| C(3)-C(2)-H(2) | 114.1(13) | C(8)-C(9)-H(9) | 118.9(13) |
| O(2)-C(3)-C(2) | 109.40(14) | C(10)-C(9)-H(9) | 120.9(13) |
| O(2)-C(3)-C(4) | 110.15(14) | C(11)-C(10)-C(9) | 120.15(17) |
| C(2)-C(3)-C(4) | 113.30(14) | C(11)-C(10)-H(10) | 119.3(12) |
| O(2)-C(3)-H(3) | 103.6(12) | C(9)-C(10)-H(10) | 120.6(12) |
| C(2)-C(3)-H(3) | 112.8(12) | C(10)-C(11)-C(12) | 119.91(17) |
| C(4)-C(3)-H(3) | 107.1(12) | C(10)-C(11)-H(11) | 119.1(13) |
| N(1)-C(4)-C(5) | 108.58(14) | C(12)-C(11)-H(11) | 120.9(13) |
| N(1)-C(4)-C(3) | 110.14(13) | C(7)-C(12)-C(11) | 120.57(18) |
| C(5)-C(4)-C(3) | 111.78(14) | C(7)-C(12)-H(12) | 120.9(13) |
| N(1)-C(4)-H(4) | 105.3(13) | C(11)-C(12)-H(12) | 118.6(13) |
| C(5)-C(4)-H(4) | 112.0(13) | | |
| C(3)-C(4)-H(4) | 108.8(12) | | |
| O(1)-C(5)-C(4) | 107.17(13) | | |
| O(1)-C(5)-H(5A) | 107.8(13) | | |
| C(4)-C(5)-H(5A) | 110.5(13) | | |

**Table A20**. Anisotropic displacement parameters ($Å^2$ x $10^3$) for $C_{12}H_{15}NO_4S$. The anisotropic displacement factor exponent takes the form: $-2\pi^2[ h^2 a^{*2}U_{11} + ... + 2 h k a^* b^* U_{12} ]$

| | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| S | 12(1) | 15(1) | 18(1) | -1(1) | 1(1) | -2(1) |
| O(1) | 17(1) | 16(1) | 16(1) | -2(1) | -2(1) | 4(1) |
| O(2) | 22(1) | 12(1) | 27(1) | 3(1) | -4(1) | -5(1) |
| O(3) | 23(1) | 16(1) | 27(1) | -2(1) | 2(1) | -6(1) |
| O(4) | 13(1) | 30(1) | 26(1) | -2(1) | 0(1) | 1(1) |
| N(1) | 14(1) | 13(1) | 17(1) | 0(1) | 1(1) | 0(1) |
| C(1) | 18(1) | 16(1) | 16(1) | -1(1) | 4(1) | -1(1) |
| C(2) | 16(1) | 17(1) | 19(1) | 2(1) | 3(1) | -1(1) |
| C(3) | 13(1) | 11(1) | 18(1) | 1(1) | 0(1) | -1(1) |
| C(4) | 13(1) | 12(1) | 17(1) | -1(1) | 1(1) | 2(1) |
| C(5) | 17(1) | 14(1) | 18(1) | -2(1) | 1(1) | 3(1) |
| C(6) | 21(1) | 20(1) | 16(1) | -1(1) | 1(1) | 3(1) |
| C(7) | 16(1) | 16(1) | 16(1) | -1(1) | -1(1) | -1(1) |
| C(8) | 19(1) | 21(1) | 18(1) | 5(1) | 2(1) | 0(1) |
| C(9) | 17(1) | 24(1) | 22(1) | 1(1) | 2(1) | 3(1) |
| C(10) | 20(1) | 20(1) | 19(1) | 0(1) | -4(1) | 2(1) |
| C(11) | 27(1) | 20(1) | 14(1) | 3(1) | -2(1) | -1(1) |
| C(12) | 23(1) | 21(1) | 14(1) | -2(1) | 2(1) | -1(1) |

**Table A21**. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$ x $10^3$) for $C_{12}H_{15}NO_4S$.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(2O) | -740(40) | 6200(30) | -1500(30) | 34(8) |
| H(1N) | -2120(40) | 2410(30) | 130(20) | 27(6) |
| H(1) | -2770(30) | 2790(20) | -3680(20) | 13(5) |
| H(2) | -110(30) | 4240(20) | -2990(20) | 11(5) |
| H(3) | 750(30) | 4090(20) | -519(19) | 8(4) |
| H(4) | -3350(30) | 4880(20) | -380(20) | 17(5) |
| H(5A) | -2620(30) | 4580(20) | 1980(20) | 14(5) |
| H(5B) | -920(30) | 5530(20) | 1530(20) | 18(6) |
| H(6A) | -180(40) | 3780(20) | 3820(20) | 17(5) |
| H(6B) | 1420(40) | 4790(30) | 3340(20) | 26(6) |
| H(8) | 4030(40) | 3110(30) | 1970(30) | 27(6) |
| H(9) | 6480(30) | 1390(20) | 2380(20) | 14(5) |
| H(10) | | 6580(30) | 0(20) | 4360(20) |
| | | 21(6) | | |
| H(11) | 3970(30) | 380(20) | 5850(20) | 16(5) |
| H(12) | 1410(40) | 2080(20) | 5380(20) | 20(6) |

**Table A22**. Torsion angles [°] for $C_{12}H_{15}NO_4S$.

| | |
|---|---|
| O(4)-S-N(1)-C(4) | -72.9(1) |
| O(3)-S-N(1)-C(4) | 157.6(1) |
| C(1)-S-N(1)-C(4) | 42.3(1) |
| O(4)-S-C(1)-C(2) | 108.2(2) |
| O(3)-S-C(1)-C(2) | -122.0(2) |
| N(1)-S-C(1)-C(2) | -8.5(2) |
| S-C(1)-C(2)-C(3) | -2.9(3) |
| C(1)-C(2)-C(3)-O(2) | -139.7(2) |
| C(1)-C(2)-C(3)-C(4) | -16.4(2) |
| S-N(1)-C(4)-C(5) | 172.6(1) |
| S-N(1)-C(4)-C(3) | -64.7(2) |
| O(2)-C(3)-C(4)-N(1) | 171.4(1) |
| C(2)-C(3)-C(4)-N(1) | 48.5(2) |
| O(2)-C(3)-C(4)-C(5) | -67.8(2) |
| C(2)-C(3)-C(4)-C(5) | 169.3(1) |
| C(6)-O(1)-C(5)-C(4) | -179.7(1) |
| N(1)-C(4)-C(5)-O(1) | 57.2(2) |
| C(3)-C(4)-C(5)-O(1) | -64.5(2) |
| C(5)-O(1)-C(6)-C(7) | -178.0(1) |
| O(1)-C(6)-C(7)-C(12) | -130.3(2) |
| O(1)-C(6)-C(7)-C(8) | 48.9(2) |
| C(12)-C(7)-C(8)-C(9) | 0.8(3) |
| C(6)-C(7)-C(8)-C(9) | -178.4(2) |
| C(7)-C(8)-C(9)-C(10) | -0.4(3) |
| C(8)-C(9)-C(10)-C(11) | -0.6(3) |
| C(9)-C(10)-C(11)-C(12) | 1.0(3) |
| C(8)-C(7)-C(12)-C(11) | -0.4(3) |
| C(6)-C(7)-C(12)-C(11) | 178.9(2) |
| C(10)-C(11)-C(12)-C(7) | -0.5(3) |

**Table A23**. Hydrogen bonds for $C_{12}H_{15}NO_4S$ [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| N(1)-H(1N)...O(2)#1 | 0.77(3) | 2.10(3) | 2.859(2) | 168(2) |

Symmetry transformations used to generate equivalent atoms: #1 –x; y-1/2; -z.